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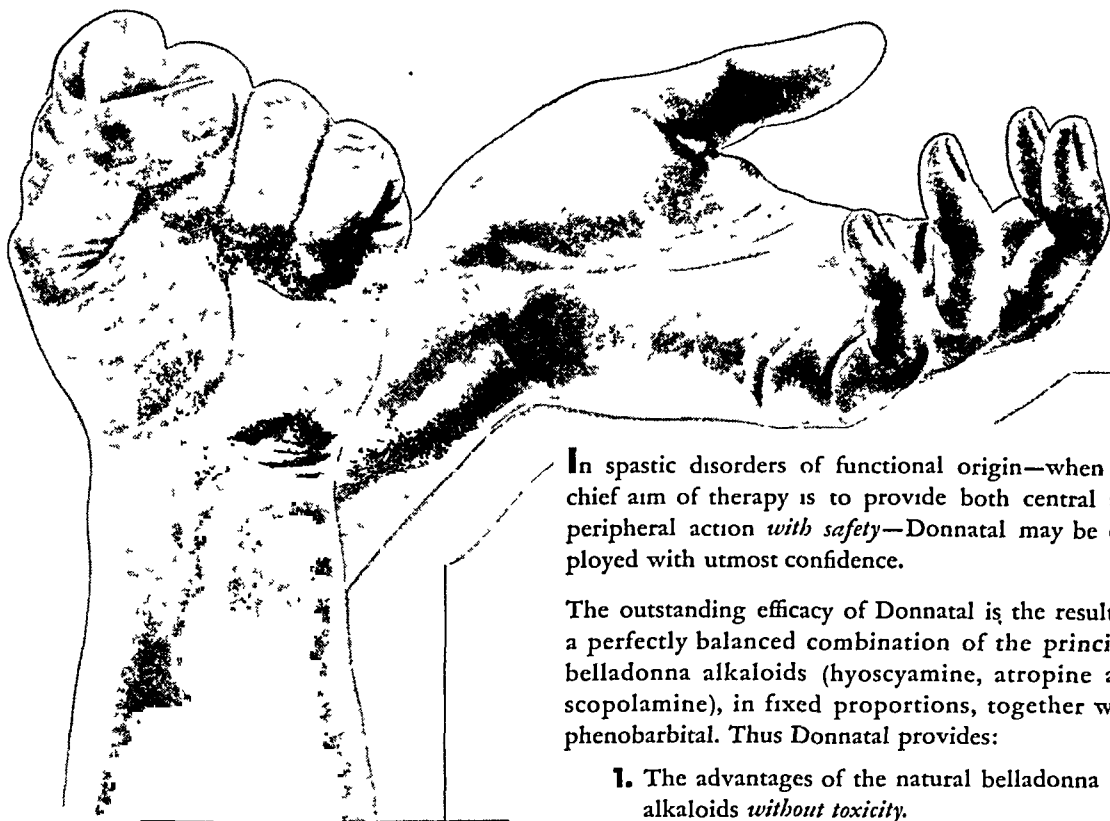
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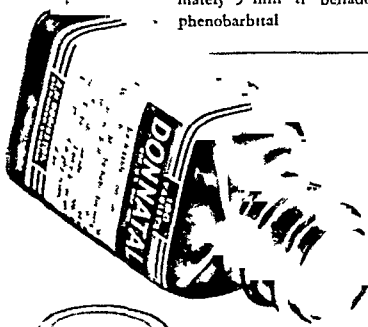
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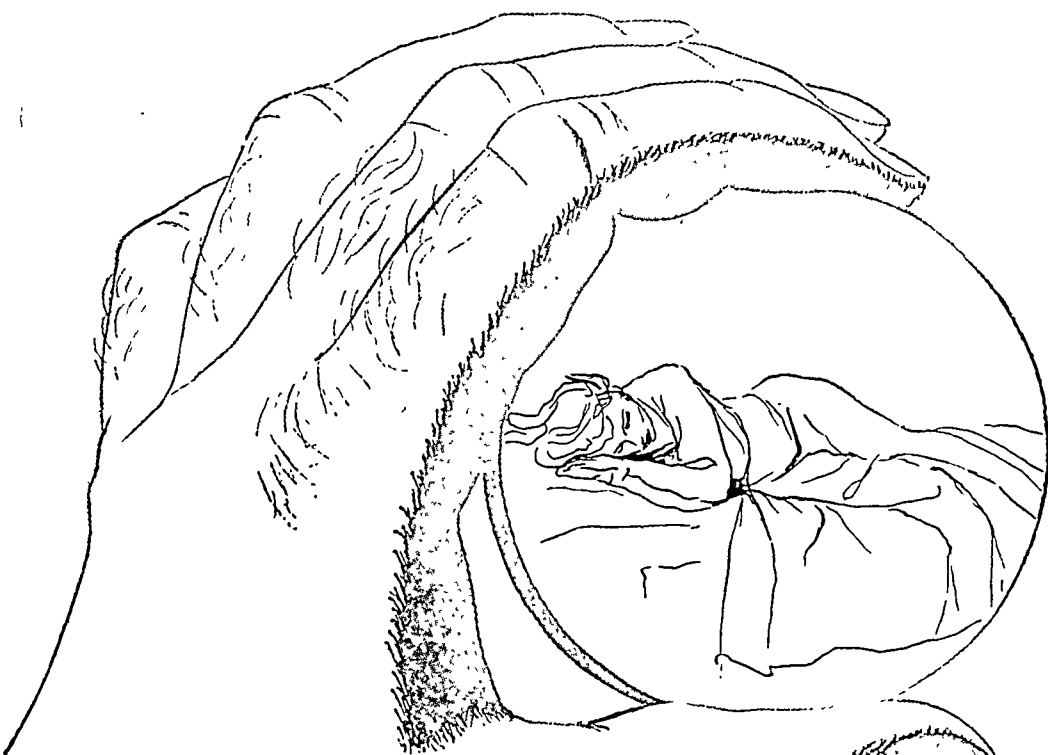
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*Simonds, F. L.: Opaque media in ex-ray diagnosis, Nebraska State M.J., 31: 326-329 (August) 1946.

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1. Canadian J. Public Health 31:428 (Sept.) 1940. 2. New England J. Med. 223:265 (Aug. 22) 1940. 3. Current Comment: J.A.M.A. 129:74 (Sept. 1) 1945.

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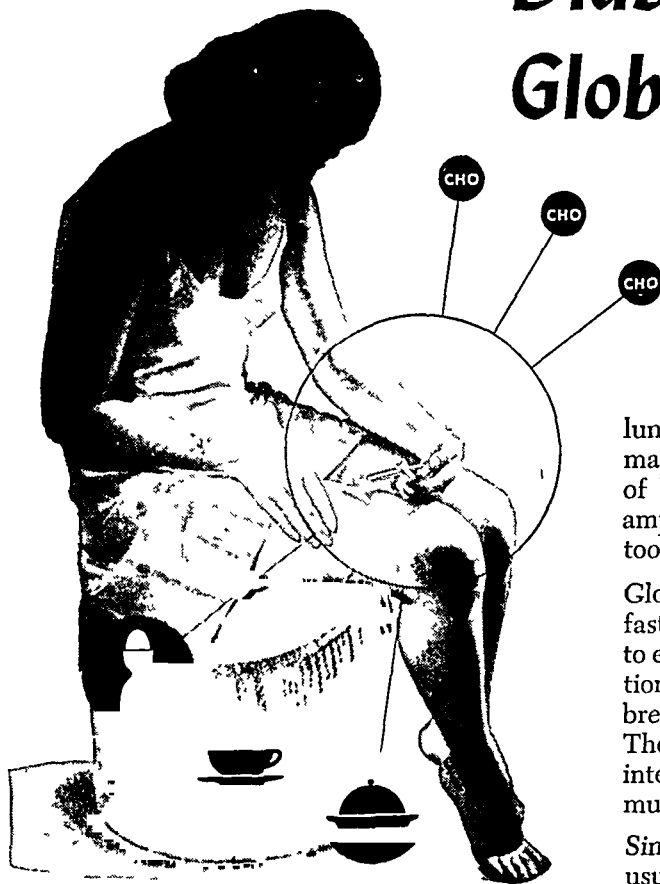
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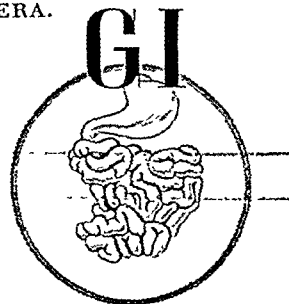
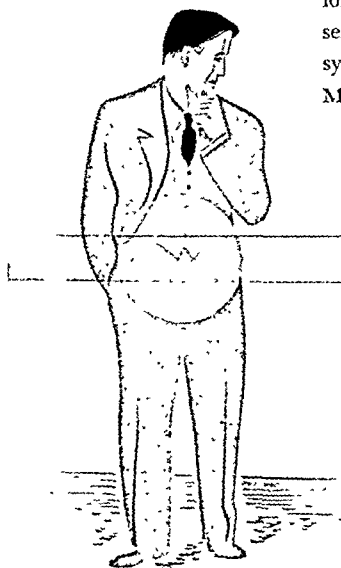
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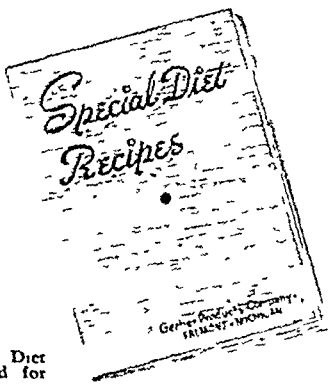
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GASTROENTEROLOGY

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VOLUME 8

February 1947

NUMBER 2

LARGE, OTHERWISE NORMAL GASTRIC RUGAE SIMULATING TUMOR OF THE STOMACH

A REPORT OF THREE CASES

WILLIAM E. RICKETTS, M.D., JOSEPH B. KIRSNER, M.D., PH.D. AND WALTER LINCOLN PALMER,
M.D., PH.D.

*From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago, Chicago,
Illinois*

7:11

INTRODUCTION

The differentiation of gastric cancer from non-malignant conditions of the stomach has been of great interest to the internist, surgeon and the roentgenologist for a long time. Attention has been directed (1, 2) to the tumor-like appearance of redundant gastric mucosa and the production of "filling defects" in the pyloric and duodenal regions caused by the prolapse of mucosa through the pylorus (3, 4). In recent years, various authors (5-13) have emphasized the marked similarity roentgenologically and gastroscopically between giant hypertrophic gastritis and carcinoma of the stomach. Reference (14, 15, 16) has been made also to the simulation of cancer by spasm of the antrum and pyloric regions of the stomach. Indeed, spastic contraction producing a roentgenological picture of constriction and rigidity of the prepyloric portion of the stomach may resemble very closely organic disease.

The purpose of this paper is to present three cases in which the appearance of gastric tumor was simulated roentgenologically by large but otherwise normal appearing gastric folds. There was no evidence, gastroscopically, of gastritis or other organic disease. In two patients the abnormality disappeared following the insufflation of air, while in the third case, the mucosal folds assumed normal size upon the subsidence of peristaltic activity.

Case 1. S. S., a 55 year old male automobile mechanic, had had frequent physical examinations since 1928 because of numerous and varied complaints. These included headaches, paresthesias, and vague pains in many parts of the body, abdominal distension, a burning sensation in the epigastrium which was present throughout the day, and not completely relieved by the taking of food and alkali, and a sense of pressure in the lower abdomen relieved by defecation. There had been no vomiting, hematemesis, melena, or loss of weight. Physical examination in April 1945 revealed a well developed and well nourished adult male with myopia, a senile cataract in the

right eye, thickening of the radial arteries, and moderate enlargement of the prostate. The erythrocyte count was 4.55 million, hemoglobin 14.0 grams, and leukocyte count 6,200. The urine was normal. Seven stool examinations were negative for occult blood. The maximum free HCl in response to histamine stimulation was 105 clinical units. The Wassermann and Kahn tests were negative. The clinical impression was that of an anxiety state with hypochondriasis. Roentgen studies revealed anoma gall bladder, esophagus, duodenal bulb, terminal ileum, and colon. The pyloric antrum, however, appeared abnormal. At no time did it fill out completely and with carefully adjusted pressure the mucosal pattern seemed coarse, irregular and suggestive of an early ulcerating neoplasm (figure 1).

At gastroscopy a normally contracting pylorus was visualized. The antrum, during peristaltic activity, presented large but otherwise normal appearing folds, a finding very suggestive of redundant gastric mucosa (Plate I-A). With subsidence of peristaltic activity, the mucosa of the antrum assumed a completely normal appearance. There was no evidence of ulceration or carcinoma. A second roentgen examination, two weeks after the original study, again demonstrated an abnormal prepyloric region. This now was interpreted as an S-shaped pylorus with rather thick musculature and unusually thick mucosal folds. The possibility of an early neoplasm was not eliminated. A completely normal gastric mucosa was visualized at a second gastroscopic examination. There was no enlargement of the mucosal folds at this time and no evidence of gastritis, neoplasm or ulceration.

The patient subsequently was observed in the gastrointestinal clinic for one year. Symptoms consisted primarily of anxiety and hypochondriasis, distress in the left hypochondrium, and substernal pain. Two electrocardiograms revealed no abnormal findings. Additional roentgen examinations, six and eleven months after the initial study, showed no change in the appearance of the stomach. The distal two inches of the pyloric antrum appeared irregular and contained coarse folds, although these were less marked than at the original examinations. Peristaltic waves traversed this region of the stomach normally. A third gastroscopic examination again revealed large but otherwise normal mucosal folds in the antrum. The digestive symptoms were relieved by the use of a bland diet, sedatives and antispasmodics.

Case 2. R. S., a 50 year old white house-wife, had experienced a "funny feeling" in the abdomen, and belching for many years. Six months previously the patient had vomited for one day. Although this symptom subsided, she consulted a local physician, who, after the completion of roentgen studies of the gastrointestinal tract (figure 2), advised the patient that she had a very extensive gastric tumor; "my stomach was all moth eaten." Apparently after this verdict the patient developed an acute anxiety state with loss of appetite and energy. However, she did not lose weight. Three weeks prior to admission, she consulted another physician who referred her for gastroscopic examination. Gastroscopy revealed (Plate I-B) thick folds, some of them curved and twisted on themselves, along the greater curvature of the stomach. The folds were not creased and the mucosal surfaces appeared normal. There was no evidence of gastric tumor or ulceration.



VIEW A

VIEW B

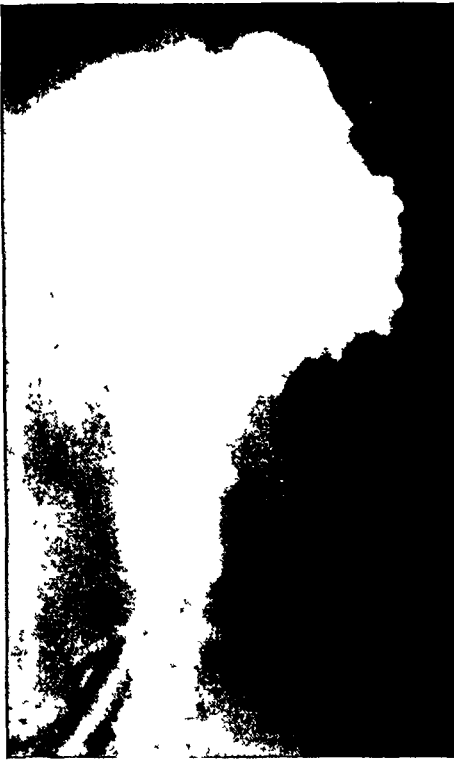


VIEW C

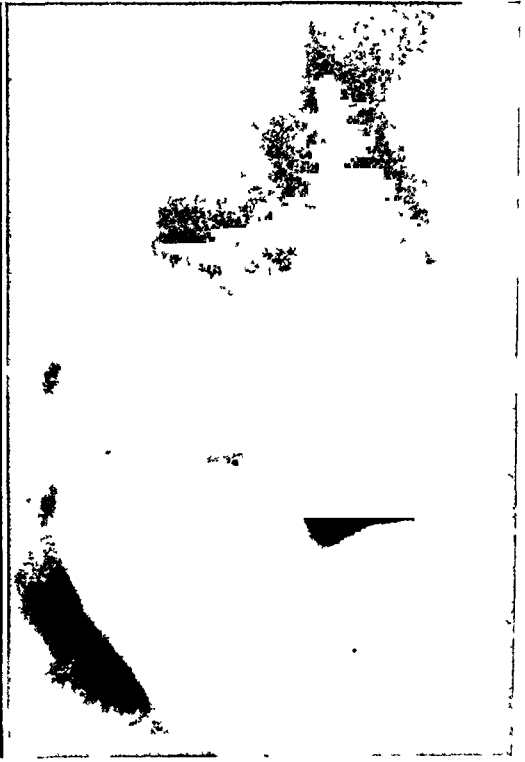
VIEW D

FIG 1. Case 1 Views A and B demonstrate an abnormal appearance of the antrum with a coarse, irregular mucosal pattern suggestive of neoplasm with ulceration

Views C and D taken on the same day The antrum is S shaped and somewhat narrowed The mucosal folds, particularly in (C) now appear normal



VIEW A



VIEW B



VIEW C



VIEW D

FIG. 2. Case 2. View A: Filling defect in the midportion of the stomach along the greater curvature. Views C and D Slightly enlarged gastric rugae.

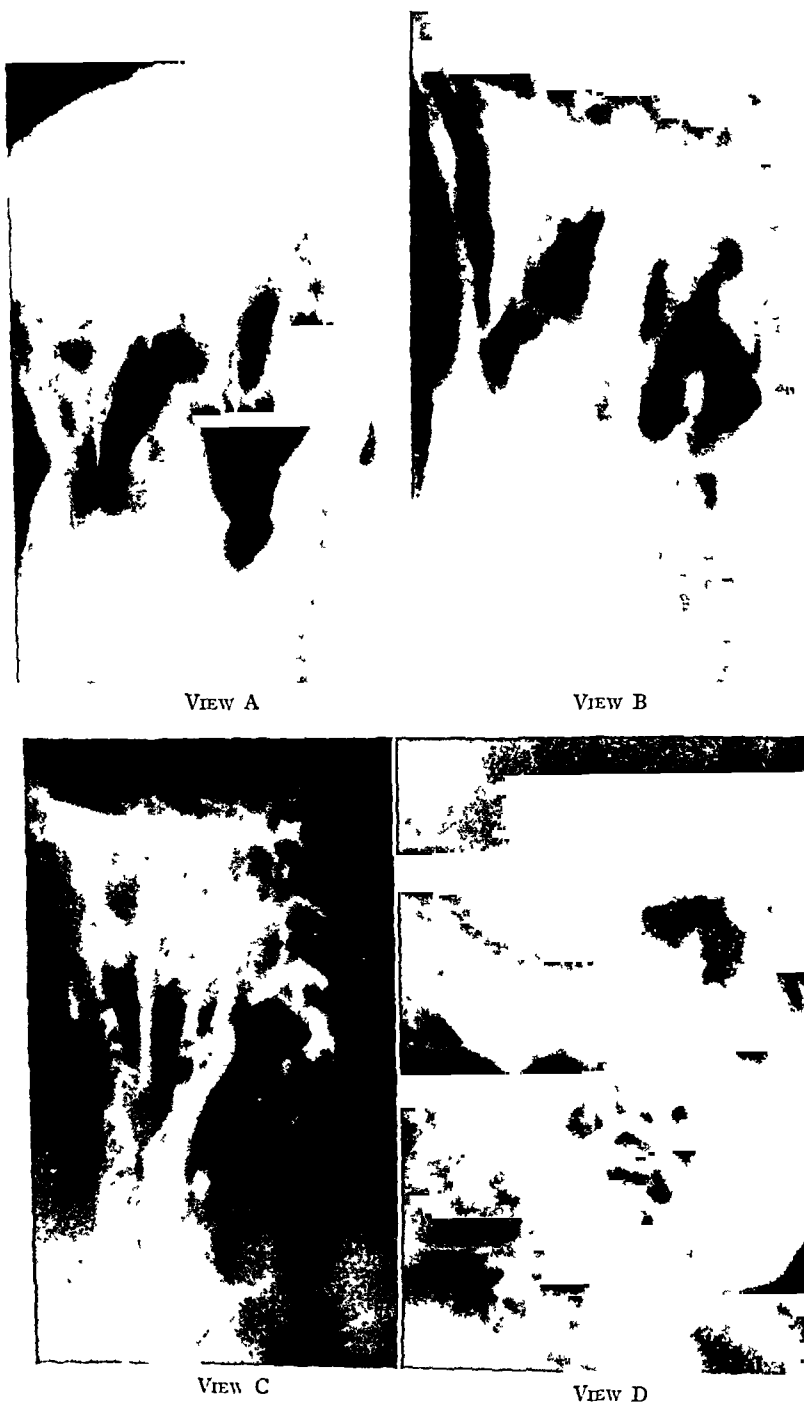


FIG 3 Case 3 Very large and coarse rugae, especially in the upper portion of the stomach.

Case 3. J. T., a 40 year old male, was first seen in January 1936 because of chronic sinusitis and bronchitis, and a history of "indigestion" for approximately ten years. Symptoms consisted of a burning sensation in the epigastrium, a sense of fullness, constipation, nervousness, headaches, and a lack of energy, frequent "colds" and an annoying cough, productive of much sputum which did not contain blood. The past medical history was not significant. Physical examination did not reveal any abnormal findings, except for a reddened, granular appearing pharynx. Routine laboratory studies were normal. The patient was not seen again for the next ten years. His mild digestive complaints had continued; during the three months preceding the present admission he had lost eight pounds in weight, although his appetite has been excellent. The red blood count was 4.62 million with 91% hemoglobin; the leukocyte count measured 10,250 and the differential smear was normal. The sedimentation rate was normal and the Wassermann test was negative. Gastric analysis (Ewald meal) revealed a free HCl of 20 clinical units. Fluoroscopic examination of the stomach elsewhere was reported to have demonstrated a neoplasm on the greater curvature of the stomach. The physical examination was normal. Roentgen study demonstrated extremely deep and coarse rugae throughout the stomach (figure 3). This finding was interpreted as an anatomical phenomenon and not gastric neoplasm; the possibility of a tumor could not be excluded, however, on the basis of a single examination. Gastroscopy revealed rather striking findings. Very large but otherwise normal appearing folds were observed in the upper portion of the stomach, especially along the greater curvature (Plate I-C). These folds disappeared almost entirely with the insufflation of air (Plate I-D). There was no evidence of neoplasm, ulcer, or gastritis. The gastroscopic impression was that of prominent, normal gastric rugae in the upper portion of the stomach.

DISCUSSION

The foregoing cases demonstrate that large normal gastric rugae may simulate, roentgenologically, the appearance of gastric tumor. Characteristically in these patients the abnormality was not constant. The rugae were very pliable and their size seemed to vary with the tonicity of the stomach. Insufflation of air and subsidence of peristalsis reduced the folds to normal size. The absence of gastritis, as noted gastroscopically, further differentiated the condition from hypertrophic gastritis. The mechanism for the production of the large rugae is not entirely clear. The studies of Forssell (17) and others indicate that the thickness of the submucosa and the action of the muscularis propria and muscularis mucosa influence the size and distribution of the folds.

The case reports of Jenkinson and Latteier (16) are of considerable interest with regard to the subject of gastric spasm. In one patient a large well circumscribed filling defect involving the pars pylorica was described roentgenologically. This defect seemed to be constant and peristaltic waves did not traverse the area. The rugae in the upper and mid portions of the stomach

appeared distorted and thickened. At operation the stomach was normal externally. Palpation of the pylorus and antrum yielded a sensation of induration. This sensation vanished entirely after a short pause, only to return upon the development of another spastic contraction of the prepyloric region. Microscopic examination of a biopsy from this area revealed normal gastric tissue and no evidence of disease. In the second case a similar defect was described roentgenologically. The abnormality was present after two days of atropine therapy and appeared unchanged at roentgen examination one month later. A partial gastric resection was performed and microscopic examination of the specimen in this case also revealed normal gastric tissue.

The presence of large rugae within the stomach simulating gastric tumor undoubtedly is more common than has been generally appreciated. Indeed, we have recently encountered a fourth case in which an irregular polypoid filling defect was observed roentgenologically in the cardiac portion of the stomach. At operation a small soft mass was palpated which proved to be redundant gastric mucosa. Microscopic examination of a biopsy from this area revealed normal gastric tissue. The patient died one year later of lobar pneumonia. Necropsy disclosed a normal stomach. Recognition of this condition obviously is desirable to avoid an unfavorable prognosis and an unnecessary hazardous operation. Gastroscopy may be particularly helpful in this regard, and together with repeated roentgenologic examinations, should lead to the proper diagnosis.

SUMMARY

Three case reports are presented in which the appearance of gastric tumor was simulated by large but normal appearing gastric rugae. The folds in two patients returned to normal size after the insufflation of air, and in the third case, upon the subsidence of peristaltic activity. The correct diagnosis was made by gastroscopy and repeated roentgenologic study. The underlying mechanism is not established, but it is presumed to be gastric spasm with increased contractility of the muscularis mucosae.

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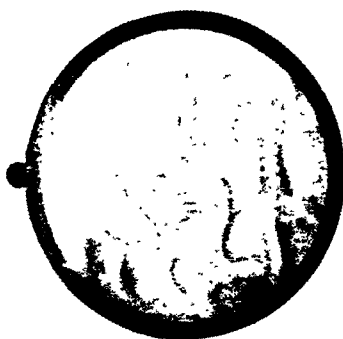
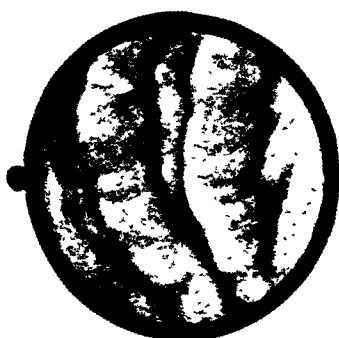
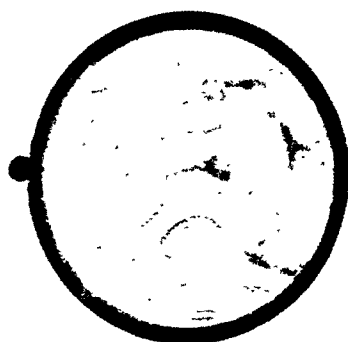


PLATE I

A. Case 1. Gastrosopic appearance of large, redundant gastric folds in the antrum, extending to the pylorus during peristaltic contraction.

B. Case 2. Gastrosopic appearance of large, tortuous rugae twisted on each other along the greater curvature of the stomach.

C and D. Case 3. (C) Very large, otherwise normal gastric folds along greater curvature of stomach *before* insufflation of air. (D) Same region *after* insufflation of air demonstrating normal sized rugae.

CRITERIA FOR GASTROSCOPIC EXAMINATION IN THE ARMY

DONALD T. CHAMBERLIN, M.D., F.A.C.P.

In the Army the patients selected for gastroscopic examination fell into three groups: first, those with well defined intragastric lesions seen by radiography, who were examined for confirmation, for teaching purposes, and to gain personal experience; second, those patients with suspicious or ill-defined lesions in the stomach, who were examined in an effort to make a more positive diagnosis; and third, and most important, the group who had persistent, disabling symptoms and normal roentgenologic findings.

The criteria were the same both here at home and overseas. In previous papers I have shown the results of our experiences at Lawson General Hospital, Atlanta, Georgia. The records of the soldiers there examined are not available to me at this time, and the present report is of a group of 168 soldiers seen at the 103rd General Hospital in England during a period of about nine months, from September, 1944 to May, 1945. Sixty-six of this group had symptoms existing prior to combat, and 102 suffered their initial symptoms during service in battle. Table 1 shows the total numbers with their gastroscopic diagnoses. It is of interest to note that the patients in the "old" group had had their symptoms for an average of five years regardless of the gastroscopic diagnosis.

One hundred and thirty-four patients were examined who had normal findings by radiography. All of these soldiers had persistent disabling symptoms referable to the upper abdomen. Their length of illness varied from a few weeks to several years but in all cases the symptoms were severe enough to cause them to be evacuated from the active zone back to general hospitals.

The psychiatrists in all the hospitals in the rear area were overwhelmed with patients with severe psychosomatic symptoms. It was in such cases that the gastroscope was most useful, both in reducing the work of the psychiatrists and in preventing some patients with organic changes of sufficient severity to account for the symptoms from getting tagged with the—to them, and to many employers—stigma of the diagnosis of psychoneurosis.

Table 2 shows this group with their diagnoses. Ninety of the group were sent to the psychiatrist for disposition and the rest were treated by the medical service; many of them returned to duty. It is worthy of note that only one of the eleven gastric ulcers in the series was diagnosed by gastroscopic examination alone, and that we were able to find the ulcer in the other ten which were demonstrable by X-ray.

The mucosal changes in the other cases of this group were of sufficient severity to account, in our opinion, for the symptoms present. Minor mucosal

changes were disregarded as within normal limits. It was only when there were definite, wide-spread and severe changes present that a diagnosis of gastritis was made. Furthermore, I insisted that a clinical diagnosis of gastritis should not be made unless it was confirmed by gastroscopy, and that a radiological diagnosis of gastritis was insufficient.

Table 3 shows the correlation of gastroscopic and radiographic findings in the group with positive X-ray studies. Patients with duodenal ulcer were considered to have a normal stomach radiologically for the purpose of this study, and

TABLE 1

GASTROSCOPIC DIAGNOSIS	ONSET PRIOR TO COMBAT*	ONSET DURING COMBAT	TOTAL
Carcinoma.....	0	1	1
Chronic superficial gastritis.....	9	12	21
Atrophic gastritis.....	5	0	5
Hypertrophic gastritis.....	10	10	20
Gastric ulcer.....	4	7	11
Normal stomach.....	35	66	101
Unsatisfactory.....	3	6	9
Total.....	66	102	168

* Average duration of symptoms in "old" cases 5 years.

TABLE 2

*Patients with negative X-ray studies with persistent symptoms. Total 134**

Normal stomach.....	90
Chronic superficial gastritis.....	13
Atrophic gastritis.....	5
Hypertrophic gastritis.....	15
Gastric ulcer.....	1

* 44 patients with mucosal changes severe enough to account for their symptoms.

are not mentioned as such, except when the radiologist found concomitant intra-gastric changes.

The majority of patients in this series were referred from other hospitals, where, in many cases the medical officer designated as radiologist was inexperienced. For this reason we required the films to accompany the patient to the 103rd General Hospital. Whenever we disagreed with the X-ray diagnosis previously made, a note to that effect was sent back with the patient's record. There were several cases of "gastric ulcer" referred to us, in which we could neither find the crater in the films nor see it on gastroscopic examination. In the analysis of this series these were considered as having normal X-ray films.

The correlation was most accurate in the cases of hypertrophic gastritis and in the ten ulcer cases where the crater was seen in the films. In the five cases in which a polyp was diagnosed by X-ray, I was doubtful about it on the films and could not find it with the gastroscope.

Thirteen patients were examined whose presenting complaint was haematemesis of recent or old occurrence. In five of these, no cause could be found, but in the other eight, there were changes wide-spread enough to account for it, though no actively bleeding areas were found. Table 4 lists these cases.

Seven patients with recurrent malaria were examined because of persistent

TABLE 3

GASTROSCOPIC DIAGNOSIS	X-RAY DIAGNOSIS				
	Crater	Hypertrophic rugae	Gastritis	Polyp	Greater curvature lesion
Normal.....	0	5	1	1	0
Chronic superficial gastritis.....	2	2	2	0	2
Atrophic gastritis.....	0	0	0	0	0
Hypertrophic gastritis.....	1	3	4	0	0
Carcinoma.....	0	0	0	1	0
Gastric ulcer.....	10	0	0	0	0

TABLE 4

Haematemesis—13 patients

DIAGNOSIS	ONSET PRIOR TO COMBAT	ONSET DURING COMBAT
Normal.....	1	4
Hypertrophic Gastritis.....	1	5
Chronic Superficial Gastritis.....	0	1
Atrophic Gastritis.....	1	0

nausea and vomiting. Three of these had chronic superficial gastritis, and in four the stomach was normal. These cases are recorded here only as a matter of interest and no inference is made regarding the relationship of gastric mucosal changes to recurrent malaria.

CONCLUSION

The analysis of the gastroscopic findings in this small series of cases demonstrates that the greatest usefulness of the gastroscope in military service lies in the scrutiny of those cases with severe disabling digestive symptoms without cause demonstrable by other methods. More accurate disposition of such cases is possible, and many patients can then be treated medically and their condition improved sufficiently so that they can return to duty.

SUMMARY

1. The gastroscope was used in the army on three classes of patients: a. those with typical intra-gastric disease who could be used for teaching purposes; b. those with obscure or doubtful lesions, for more accurate diagnosis; and c. those without roentgenologically demonstrable disease, in order to make a diagnosis.

2. An analysis of 168 cases is made.

3. By use of the gastroscope certain patients may be spared the tedious effort of psychotherapy and the stigma of the diagnosis of psychoneurosis.

AMEBIASIS: OBSERVATIONS IN AN ARMY GENERAL HOSPITAL IN INDIA*

KENDALL A. ELSOM, M.D., ARTHUR M. ROGERS, M.D., AND FRANCIS C. WOOD, M.D.

From the Medical Clinic of the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

INTRODUCTION

Amebiasis was one of the chief medical causes for disability in the China-Burma-India theatre. In the 20th General Hospital, located on the north-eastern India-Burma border at Ledo, Assam, well over 1000 cases were seen in a 2 year period. The diarrhea-dysentery group as a whole ranked third as a cause for admission to the Medical Service, amebiasis constituting 45 per cent of this group.

During the early months of operation limitations in time, personnel and equipment did not permit a planned study of amebiasis. As the facilities improved a group of dysentery wards was established which made possible more careful and detailed study of all cases coming under our personal supervision. It is the purpose of the present communication to describe some of the outstanding impressions which resulted from a large experience gained during the exigencies of military practice, and to present data derived from a detailed analysis of 382 cases occurring, without a fatality, in American soldiers in the 21 month period from April 1943 to January 1945.

Classification:

Our cases fell into 6 main groups, as follows:

I. Amebic dysentery (primary attack) ¹	258
a. Acute (symptoms less than 1 week)	93
b. Subacute (symptoms 1 to 4 weeks)	72
c. Chronic (symptoms over 4 weeks)	93
II. Recurrent amebic dysentery	10
III. Mixed dysentery, amebic and bacillary	8
IV. Amebic hepatitis	30
V. Amebic hepatic abscess	4
VI. "Asymptomatic" amebiasis	72
Total	382

* Presented at the meeting of the American Gastroenterological Association, May 24 and 25, 1946, Atlantic City, New Jersey.

¹ The terms "acute", "subacute" and "chronic" are used in this paper to designate the duration of symptoms prior to hospitalization, not the suddenness of onset or the severity of the disease. Most of the cases with a fulminating onset appear in the "acute" group because the severity of symptoms brought the patient to the hospital shortly after the illness began.

I. AMEBIC DYSENTERY

A study of tables 1 and 2 indicates that regardless of the duration of the disease the presenting symptoms of amebic dysentery were the frequent passage

TABLE 1
Symptoms recorded in 258 cases of amebic dysentery

	ACUTE (93 CASES)	SUBACUTE (72 CASES)	CHRONIC (93 CASES)
Average duration (days).....	3.6	16	80
Maximum no. stools per day (average) before hospitalization.....	8	10	9
Loose stools.....	86 (92%)	71 (98%)	91 (98%)
Abdominal pain.....	68 (74%)	51 (72%)	65 (70%)
Blood in stools.....	35 (38%)	57 (80%)	61 (65%)
Mucus in stools.....	31 (34%)	44 (61%)	59 (63%)
Nausea, vomiting, anorexia.....	27 (29%)	12 (17%)	12 (13%)
Fever.....	19 (21%)	9 (12%)	9 (10%)
Tenesmus.....	3 (4%)	8 (11%)	9 (10%)
Chills.....	9 (10%)	5 (7%)	2 (2%)
Weight loss.....	0	3 (4%)	14 (15%)

TABLE 2
Physical signs in 258 cases of amebic dysentery

	ACUTE (93)	SUBACUTE (72)	CHRONIC (93)
Admission temperature (average).....	99.3	98.6	98.8
Maximum temp. in hosp. (average).....	100.2	99.4	99.5
No fever over 99°.....	49 (52%)	57 (80%)	68 (73%)
Duration of dysentery after admission (days) (ave.).....	8.5	9	9
Max. no. of stools per day after admission (ave.).....	6	6.5	5.5
Abdominal tenderness			
Left lower quadrant.....	45 (48%)	36 (50%)	52 (56%)
Right lower quadrant.....	35 (35.5%)	25 (34.5%)	54 (58%)
Generalized.....	21 (22.5%)	10 (14%)	14 (15%)
Hepatic.....	9 (9%)	22 (30.5%)	18 (19%)
Other.....	10 (10.7%)	7 (9%)	6 (6.5%)
Hyperactive peristalsis.....	21 (22.5%)	15 (20%)	0
Malnutrition.....	0	0	6 (6.5%)
Number of cases with negative physical examination.....	34 (37%)	32 (45%)	39 (42%)

of loose stools, usually containing blood and mucus, associated with cramp-like abdominal pain. Fever, chills, nausea, vomiting and tenesmus were exceptional. On physical examination approximately 40 per cent of the patients

had no significant abnormalities, in the remaining 60 per cent low grade fever, abdominal tenderness, most commonly in the left or right lower quadrant but often generalized, usually constituted the only positive signs. The maximum number of daily bowel movements during hospitalization was, on the average, only 6. Dehydration and malnutrition were strikingly absent. Amebiasis was not a prostrating disease. Only an occasional patient considered himself ill enough to stay in bed, the majority remaining ambulatory throughout their illness.

A mere tabulation of the symptoms and signs, with their relative frequencies, fails, however, to convey the impression of what in our experience was an outstanding characteristic of amebic dysentery, i.e. the extreme variability in the severity of the disease. At one extreme were 10 per cent of the group who described having from 10 to 30 stools a day associated with nausea, vomiting, severe abdominal pain, chills and fever. On admission an individual in this category might have a temperature of 104°F., extreme abdominal tenderness, a leukocytosis of 20,000, and an almost hourly evacuation of bloody feces. Such a clinical picture was indistinguishable from that of acute bacillary dysentery.

At the other extreme was a group of patients who were almost asymptomatic. They had come to the hospital in many instances because of some other illness or because of an injury. A routine stool examination disclosed *E. histolytica*, and only after close questioning was a history of mild, chronic diarrhea obtained. In civilian practice these patients would not have sought hospitalization for their abdominal complaints. It was often difficult to decide whether they should be classified as asymptomatic carriers or true cases of dysentery. They were afebrile, normal on physical examination, and were passing only 1 or 2 stools daily. Between these two extremes were so many intermediary variations that the "average" case of amebic dysentery is difficult to describe.

A further characteristic of amebic dysentery deserves consideration. Fourteen per cent of the "chronic" group, i.e. with symptoms for several months before hospitalization, stated that prior to admission they had frequently had 20 or more stools daily. One would expect that diarrhea or dysentery of this severity would soon result in prostration. It was an outstanding fact, however, that the constitutional symptoms associated with amebic dysentery were often so minimal, and the disability produced by it so slight that in spite of the great frequency of bowel movements general health was unimpaired for many weeks.

Laboratory findings

Stool examination. The stool in amebic dysentery characteristically consisted of semi-formed fecal material surrounded by blood and mucus. In the more acute cases the stool was often watery, but consisted primarily of feces.

This was in contrast to acute bacillary dysentery where odorless, blood-tinged mucus without any trace of feces was characteristically observed after the first day. This difference in the gross appearance of the specimens often suggested a correct differential diagnosis between these two diseases, but could not always be relied upon since in the very acute cases of amebic dysentery the stools were occasionally indistinguishable from those of bacillary dysentery.

The importance of the careful and prompt selection of the stool specimen in facilitating the laboratory diagnosis of amebic dysentery has been emphasized repeatedly, and deserves further mention here. Motile amebae were found most frequently in the bloody mucus surrounding the stool rather than in the fecal material itself, and much unnecessary work could be eliminated by examining only that portion of the stool. Since not every stool from a given patient with amebic dysentery contained blood and mucus it was found pref-

TABLE 3
Laboratory findings in 258 cases of amebic dysentery

	ACUTE (93)	SUBACUTE (72)	CHRONIC (93)
Stool Examination			
Trophozoites of <i>E. histolytica</i>	93 (100%)	72 (100%)	93 (100%)
Trophozoites found on 1st. exam.....	67 (72%)	46 (65%)	70 (75%)
Blood Examination			
Hemoglobin (average).....	13.8 gms.	14.9 gms.	15 gms.
WBC per cu. mm. (average)	8,800	10,000	8,800
Polys %.....	63	65	64
Lymphs %.....	32	30	30
Monos %.....	2	2	3
Eosin %.....	3	3	3

erable to limit the microscopic examination to those which did. It was further observed that the percentage of positive stool examinations was materially greater when liquid or semi-liquid feces was obtained. We, therefore, adopted the policy of administering a cathartic to those patients, encountered with surprising frequency, who were suspected of having amebic dysentery but who were passing solid stools.

A positive laboratory diagnosis was made on the first direct stool examination in approximately 70 per cent of cases (table 3). In the remaining 30 per cent from 2 to 5 examinations were required. If 5 careful examinations of properly selected material failed to reveal *E. histolytica* the chance of success on subsequent examinations was very small.

Blood examination. The data in table 3 require no elaboration. It will be observed that only in acute amebic dysentery was there any evidence of

anemia, and this was not severe enough to be of clinical significance in the average patient. The absence of leukocytosis, or disturbance in the differential count was striking. Eosinophilia was not a characteristic finding in amebic dysentery. While eosinophile incidence of 20 per cent was occasionally observed other causes, especially intestinal parasites, were frequently present.

Proctoscopic findings. The proctoscopic findings in 39 patients with amebic dysentery who were examined prior to, during, and on completion of treatment were analyzed for the present report. In 32, or 82 per cent, definite abnormalities were observed (table 4). They were, in general, clear-cut and easily visible in those individuals who were having active dysentery. The character of the lesions bore no apparent relationship to the duration of the disease prior to the treatment. The most typical lesion was a small, shallow, irregular ulceration from 2 to 4 mm. in diameter, surrounded by a narrow zone of erythema and

TABLE 4
Proctoscopic findings in 39 cases of amebic dysentery

	ACUTE (6 CASES)	SUBACUTE (7 CASES)	CHRONIC (26 CASES)	TOTAL (39 CASES)
Positive findings	5 (83%)	7 (100%)	20 (77%)	32 (82%)
(a) Mild, inflamed areas with mucus and blood only	1	1	0	2
(b) Moderate; shallow ulcerations or erosions	2	5	16	23
(c) Severe, deep ulcerations, extensive membranous exudates or strictures	2	1	4	7
No positive findings	1 (17%)	0 (0%)	6 (23%)	7 (18%)

usually covered with a thin gray, membranous exudate, which bled easily on trauma. These lesions were multiple, as many as 4 or 5 being seen in one field of vision, and were most numerous in the rectum and rectosigmoid. This type of superficial ulcer was quite constant in appearance from patient to patient, and was sufficiently characteristic of amebic dysentery to suggest the diagnosis at a glance even though a positive diagnosis was made only after microscopic demonstration of amebae. Less frequent though of greater clinical import were larger, deeper ulcers, frequently solitary. These lesions were from 1 to 2 cm. in diameter as a rule, and were covered with an adherent gray membrane. The extent and depth of the ulcers was usually apparent only when the membrane had sloughed away after a few days of treatment. Both types of ulcerative lesions were clearly circumscribed and the intervening mucosa was usually essentially normal. In only 3 instances a diffuse inflammation of the rectal mucosa was observed.

In 22 of these 39 patients an attempt was made to recover motile amebae from the ulcerative lesions. It was successful in 17 instances. The method of choice was the use of a 1.0 c.c. pipette furnished with a small aspirator. The tip of the pipette was placed directly on the lesion under proctoscopic observation, and with mild suction a few cu. mm. of fluid were aspirated from the base of the ulcer. Immediate examination of this material frequently revealed motile amebae in patients in whom repeated stool examinations had been negative.

The response of the ulcerative lesions to treatment was observed by repeated proctoscopic examination. After 2 or 3 days motile amebae were no longer obtainable from the shallow ulcers, which healed rapidly. After 10 to 14 days of treatment usually no trace of these lesions was visible. The deeper ulcers healed more slowly, requiring 4 to 6 weeks. White stellate scars sometimes remained at the site of the deeper lesions. Two patients with large, deep rectal ulcers developed rectal strictures. The first patient was examined prior to and frequently during the course of treatment. On admission he had an extensive granulomatous ulcer between the second and third plica semilunaris involving the entire circumference of the rectum. Biopsy revealed amebae invading the tissue. The ulcerative lesion gradually disappeared after two months of treatment, leaving a stricture which would not permit the passage of a proctoscope. When the patient left the hospital a month later to return to the U. S. the stricture was still present. A report several months later stated that the lesion had disappeared, and that the soldier had returned to duty.

The second patient was first examined several weeks after treatment had been begun. A large ulcer was seen at the level of the first plica semilunaris. As healing occurred the bowel lumen became markedly constricted, and the stools were ribbon-like. He was still under treatment several months after his return to the U. S. Both patients had a negative Frei test.

The Barium Enema. The colon was visualized radiographically in 92 patients with amebiasis. The results will be reported elsewhere (1). Twenty-one of the patients had irritability of the colon. In 7 this was particularly noted in the cecum, but the observed changes were in no way diagnostic. In only two instances could the radiological diagnosis of mucosal ulceration of the colon be made, and the barium enema failed to reveal the rectal ulcerations which were easily observed by proctoscope. In our opinion barium enema examination did not yield sufficient information to justify its adoption as a routine procedure in uncomplicated acute dysentery.

Differential diagnosis. In this locality, the diseases which had to be differentiated from amebic dysentery were bacillary dysentery, idiopathic diarrhea, the dysentery of malaria, and diarrhea from parasitic infestation, notably hookworm disease and strongyloidiasis. As indicated earlier, the acute form

of amebic dysentery could not at times be distinguished clinically from bacillary dysentery. Usually, however, the onset of amebic dysentery was less violent, the symptoms had existed for weeks rather than for hours, the maximum number of bowel movements per day was characteristically 5 to 10 rather than 15 to 20, as in bacillary dysentery. High fever, prostration, and intense abdominal pain were less frequent, the leukocyte count was more apt to be normal or only slightly elevated, the stools, as stated earlier, consisted primarily of feces rather than of odorless, bloody mucus. Bacillary dysentery tended to subside promptly whatever the method of treatment, while amebic dysentery usually continued unabated or only slightly improved until specific treatment was instituted. Idiopathic diarrhea could usually be distinguished by its more explosive onset, by its tendency to affect simultaneously a number of men in the same organization, by the absence of blood in the stools and by its rapid subsidence within 24 to 48 hours. Malaria was occasionally associated with bloody dysentery. The abrupt onset of chills, a remittent fever of 104°F. or above, headache and generalized bone, joint and muscle pains were so characteristic of it, and so atypical of amebic dysentery that their differentiation was not difficult. Hookworm disease and strongyloidiasis frequently gave rise to low-grade generalized abdominal pain and diarrhea. These diseases did not cause bloody stools and the abdominal symptoms were usually less obviously colonic in origin, consisting rather of generalized or upper abdominal discomfort, with indigestion.

"Clinical" amebic dysentery. In spite of painstaking diagnostic effort we frequently encountered patients in whom the diagnosis of amebic dysentery was suspected on clinical grounds but was never verified in the laboratory. In 70 cases not included in this analysis we were obliged to make a diagnosis of "clinical" or "probable" amebic dysentery, hence in 21 per cent of the patients with the clinical picture of amebic dysentery, the diagnosis remained unconfirmed by laboratory studies. These patients did not differ from those described above. They suffered from dysentery of varying severity, many had blood and mucus in their stools, some gave a history of previously proved amebic dysentery, the majority had low-grade fever and abdominal tenderness. The discovery of rectal ulcers on proctoscopy suggested amebiasis in two instances. In spite of the suggestive clinical syndrome, repeated stool examinations, as many as 10 in some instances, failed to reveal *E. histolytica*. After making as thorough a diagnostic search as was feasible under the circumstances we proceeded with anti-amebic therapy. The results of treatment were not as satisfactory in this group as in proved cases of amebic dysentery, suggesting that the clinical diagnosis was in error in some instances. The large size of this group of "probable" cases indicates the frequency with which a clear-cut

diagnosis in diarrheal-dysenteric diseases could not be made even after careful study.

The treatment of amebic dysentery. Emetine hydrochloride, 0.065 gm. (1 grain) daily, administered either intramuscularly or subcutaneously, for 7 to 9 days, together with carbarsone, 0.250 (4 grains) three times daily, by mouth for 10 days, were used in the great majority of cases (table 5). Vioform, 0.250 gm. (4 grains) 3 times daily by mouth for 1 week, following the course of emetine and carbarsone, was employed in approximately 10 per-cent of the patients. Chiniofon was rarely used, being unavailable in the early months, and frequently producing abdominal cramps, indigestion and an increase in the number of stools.

The intramuscular injection of emetine was practically uniformly followed by pain for several days at the site of injection. This was often quite severe, and was occasionally followed by local induration, redness and swelling. The

TABLE 5
Treatment of 258 cases of amebic dysentery

		ACUTE (93)	SUBACUTE (72)	CHRONIC (93)
Emetine Hcl. total average dose (grains)		7.4	7.3	7.0
Carbarsone total average dose (grams)		6.4	7.0	7.5
Duration of dysentery after beginning treatment (days)		8.5	9	9
Duration of hospitalization (days)		17	18	19
Condition on discharge				
Well.	231 (90%)	84 (90%)	66 (91%)	81 (87%)
Improved	27 (10%)	9 (10%)	6 (9%)	12 (13%)

inflammation was treated by the application of heat. In no case did abscess formation occur. Emetine injected subcutaneously seemed to produce less local irritation and the drug was preferably administered by this route. An occasional patient became nauseated following the injection of emetine. This could usually be avoided by giving the drug in 2 daily doses of 0.030 gm. (gr. $\frac{1}{2}$). This practice was otherwise considered undesirable since it doubled the number of painful injections.

The potential toxicity of both emetine and carbarsone is well recognized. We were on the alert for clinical evidences of it and found none. The toxic effects of emetine on the myocardium have been especially emphasized. In no instance did cardiac symptoms or signs develop to suggest the diagnosis of emetine poisoning. The patients were restricted to the wards early in the disease but if symptoms were mild they were not kept in bed while emetine medication was in progress. The majority of patients was ambulatory

throughout hospitalization without evident ill effects. Carbarsone was uniformly well tolerated and produced no detectable toxic effects.

Early results of treatment. The immediate results of treatment were highly satisfactory, the control of symptoms was usually prompt, and in many instances dramatic. The dysentery was completely controlled in 8 or 9 days on the average. Ninety per cent of the patients were regarded as well on discharge and the remaining 10 per cent were improved. Proctoscopic studies, described earlier, bore out the clinical impression that a single course of treatment usually resulted in complete healing of the colonic lesions during hospitalization. Post-treatment stool examinations were uniformly negative for cysts or trophozoites of *E. histolytica*. The immediate results of treatment, judged by the rapidity with which the dysentery subsided, the duration of hospitalization and the condition of the patient on discharge, were equally good whatever the duration of symptoms prior to treatment. It is recognized, however, that our series did not include extremely chronic cases, which are known to be resistant to treatment.

Late results of treatment. A follow-up examination was made of 84 men who had previously been treated for amebic dysentery in this hospital from 3 to 23 months (ave. 11 months) previously. The study consisted of (a) a detailed history of bowel habits, subsequent attacks of diarrhea or dysentery, the recurrence of abdominal pain, or rectal complaints, rehospitalization or attendance at sick call and changes in weight, (b) physical examination with particular attention to abdominal tenderness and hepatic enlargement, (c) proctoscopic examination, (d) blood count, (e) examination of the stool by the direct and concentration methods. The results are summarized in table 6 and require little comment. No instance of clinical relapse or recurrence was found. All but one soldier considered himself cured. The frequent interim history of abnormal bowel habits, and periods of abdominal pain and diarrhea might suggest that complete cure had not occurred. However, the incidence of these complaints was no higher than in a similar group of well soldiers in this locality, where recurrent non-specific diarrhea was almost the rule. In American troops in this area the cyst carrier rate was known to be 10 per cent, so that the 3 per cent incidence of carriers in this small group was lower than usual.

Further evidence of the efficacy of treatment was available from an analysis of the cases returned to the United States because of amebiasis. In the first 18 months covered by this report practically all patients from China, Burma or northeast India who were returned to the United States for medical reasons did so only after evaluation in this hospital. Therefore, in addition to our own patients we saw any of those from other hospitals who were considered unfit for duty because of amebiasis or its complications. It is noteworthy that in

the entire two year period only 6 patients were returned to the United States for this reason. The standard treatment of amebic dysentery was, therefore, considered to be highly satisfactory in terms of both immediate and late results.

II. RECURRENT AMEBIC DYSENTERY

In only 4 per cent of all cases of amebic dysentery were recurrences observed. This group consisted of 10 patients, 4 of whom had been originally treated in

TABLE 6

Total follow-up examinations.....	84
Acute.....	35
Subacute.....	20
Chronic.....	29
Total follow-up period 3-6 months.....	25
6-12 months.....	24
12-23 months.....	35
History—Abnormal bowel habits.....	9
Periods of diarrhea.....	36
Abdominal pain.....	19
Sick call attendance.....	7
Weight—loss.....	6
gain.....	45
Hospitalization for diarrhea.....	1
Physical Examination—Liver palpable.....	3
Liver tender.....	1
Colon tender.....	10
Stool Examination—Trophozoites of <i>E. Histolytica</i>	0
Cysts of <i>E. Histolytica</i>	2
Sigmoidoscopic Examination—Active lesions.....	0
Healed scars—definite.....	3
possible.....	3
Blood Examination—W.B.C. (ave.).....	7,900
Hb. (gms.) (ave.).....	15.6
Total with history or findings suggesting a recurrence of amebic dysentery or chronic dysentery during the follow-up period.....	0

this hospital, the remaining 6 had previously been treated elsewhere. In half of the cases no doubt of the diagnosis of recurrent amebic dysentery existed, since the initial course of treatment had not eradicated the disease. In the others an asymptomatic period of several weeks had followed the initial treatment. In spite of the possibility of re-infection in this latter group it seems preferable to regard the dysentery as recurrent. The symptoms, physical signs and laboratory studies on readmission did not differ significantly from those already described. In every instance the stools contained trophozoites of *E. histolytica*.

The details of the treatment of the initial attack were unfortunately available in only 4 patients treated originally in this hospital, the remainder had been hospitalized elsewhere and were unaware of their exact treatment. Three of the 4 patients initially treated by us had received the standard course of emetine and carbarsone, 1 had received carbarsone only, in an inadequate dosage. Since the treatment of amebiasis was thoroughly standardized by directives from the Surgeon General we assumed that the patients treated elsewhere had received adequate therapy. In this small group, therefore, the usual treatment resulted in therapeutic failure. The fact that it constituted so few cases further emphasizes the fact that the usual treatment was very satisfactory.

III. MIXED DYSENTERY, AMEBIC AND BACILLARY

Infection both with amebae and one of the bacillary dysentery group was encountered in 8 instances. In 5 the onset of dysentery was sudden, with fever and abdominal cramps, characteristic of bacillary infection and the subsequent course likewise suggested bacillary dysentery. The amebiasis did not detectably influence the initial clinical picture or the rate of recovery. Two patients presenting the picture of amebic dysentery, with no fever and very mild diarrhea, might have been *Shigella* carriers. One patient, admitted with amebic dysentery, developed acute bacillary dysentery during hospitalization, so that the two diseases were consecutive rather than concurrent. In this small group the combination of diseases did not appear to aggravate the symptoms of either, to complicate the treatment or to prolong hospitalization. All cases responded well to anti-amebic drugs and sulfonamides, and the average period of hospitalization was 18 days, exactly that of the usual case of amebic dysentery.

IV. AMEBIC HEPATITIS

This manifestation of amebiasis was diagnosed 30 times in our series of cases. The patients fell into 2 distinct groups, 15 in each: (a) those in whom hepatitis was the primary and outstanding clinical feature, and (b) those in whom it was an incidental finding in the course of dysentery.

The patients in the first category presented a dramatic clinical picture which was characterized by the abrupt onset of severe symptoms. Intense pain in the right upper abdomen, the epigastrium or in the right lower chest was the most frequent initial symptom. It was apt to be increased on deep inspiration, and was sometimes referred to the right shoulder. A history of chills and fever was common. It was outstanding that dysentery was not a usual symptom. Only 3 of our 15 patients gave a history of dysentery in the past or on admission. It cannot be too strongly emphasized that a negative history in this regard by no means excludes the possibility of amebic hepatitis. On physical

examination the patients appeared very ill. The majority had a tender mass in the right upper abdomen, with rigidity of the rectus muscle which made identification of the underlying mass difficult or impossible. The most useful single physical sign was the complaint of intense pain on bi-manual compression of the lower right thorax. On occasion this was accompanied by pain in the right shoulder. The right diaphragm was elevated in approximately one-half of the cases. In 2 instances a transitory friction rub was heard over the right lower chest. Jaundice was not present in any case.

The average maximum temperature was 102°F.; 1 patient developed a temperature of 105°F. The average leukocyte count was 14,000; the maximum was 24,000. Strangely enough abnormality in the differential count was not usually observed. The stool examination revealed trophozoites of *E. histolytica* in only 3 instances, and cysts in 1, although an average of 3 examinations was made. Intensive study of the stools prior to treatment was not feasible since most patients had no dysentery and the use of cathartics was considered inadvisable. Decision respecting treatment could not be postponed for several days pending the results of stool examinations. Radiological examination was helpful in demonstrating elevation and limitation in motion of the diaphragm and in ruling out the possibility of a ruptured viscus. The most difficult diagnostic decision was whether or not the symptoms and signs were such that immediate surgical treatment was indicated. Ruptured peptic ulcer, acute cholecystitis, with or without rupture of the gall bladder, non-amebic hepatic abscess, acute pancreatitis and appendicitis were the chief surgical conditions considered. Malaria, renal colic and pleurisy were among the non-surgical possibilities usually noted. Early in our experience with the clinical syndrome of acute amebic hepatitis it seemed at times inadvisable to delay surgical treatment long enough to permit a trial of anti-amebic therapy. As a consequence laparotomy was occasionally performed in cases where in all probability anti-amebic therapy alone was indicated. On the other hand, it was constantly necessary to guard against the assumption that the syndrome of fever, right upper abdominal pain and leukocytosis could safely be attributed to amebic hepatitis, since this decision usually implied that 2 or 3 days, vital from the surgical standpoint, would elapse before the results of medical therapy were finally evaluated. Our caution was increased by having encountered a patient with a ruptured peptic ulcer, and another with acute calculous cholecystitis, in whom a tentative diagnosis of amebic hepatitis had been made, and in whom delay in surgical treatment might have been extremely unfortunate.

The diagnosis was necessarily made on clinical signs alone and its correctness was determined by the response of the patient to anti-amebic therapy. Emetine, 0.065 gm. (gr. 1) daily subcutaneously or intramuscularly for 7 to 10 days,

was administered as soon as the diagnosis was made. Carbarsone, 0.25 gm. (gr. iv) 3 times daily for 10 days by mouth, was given either concurrently or on completion of the course of emetine. Only rarely did the response to these drugs leave any doubt as to the true nature of the disease. Improvement was usually prompt and unmistakable. It was manifested by subsidence of fever, (chart 1), and decrease in the upper abdominal pain. The patients usually had a definite decrease in pain within 24 hours. Marked subjective improvement often preceded the subsidence of fever by 48 hours or more. Definite decrease in the size of the liver was usually noted, though this did not occur as promptly as did the loss of hepatic tenderness. The leukocyte count returned to an average figure of 9,000 on completion of treatment. The average period of hospitalization was 28 days, compared to 18 days for patients with amebic dysentery.

The second group of patients in which mild hepatitis complicated amebic dysentery presented no particular problems in diagnosis or treatment. All patients in this category were admitted because of dysentery. Either on admission, or during hospitalization, it was observed that the liver was tender and usually slightly enlarged. The tenderness was best elicited by compression of the ribs over the right lower thorax, by fist percussion over the hepatic area, or by deep palpation in the right upper abdominal quadrant. Attention was usually drawn to the possibility of hepatitis by the objective finding of hepatic tenderness rather than by the spontaneous complaint of pain. In 4 of the 15 patients the dysentery was proved to be amebic in origin, in the remainder the diagnosis of amebiasis was based on the prompt subsidence of dysentery and the disappearance of liver enlargement and tenderness following a course of anti-amebic therapy. This condition presented no difficulties in diagnosis, did not discernably alter the favorable response to treatment or increase the period of hospitalization. It was, in short, of no great clinical significance.

Late results of the treatment of amebic hepatitis were evaluated in 9 patients who were re-studied, on the average, 13 months following the original attack. Two patients had had recurrent attacks of diarrhea. Four had observed intermittent periods of right upper quadrant abdominal discomfort, especially on jarring, and in these individuals the liver was palpable 1 to 2 fingers breadths below the costal margin, and was tender on palpation. The physical examination was otherwise uniformly negative. Blood counts, stool and proctoscopic examinations were negative in every case. The results of therapy in amebic hepatitis were not considered as satisfactory as in amebic dysentery. Whether the residual symptoms and hepatic enlargement were indicative of persisting amebic hepatitis or were due to the presence of small hepatic abscesses is a matter of conjecture.

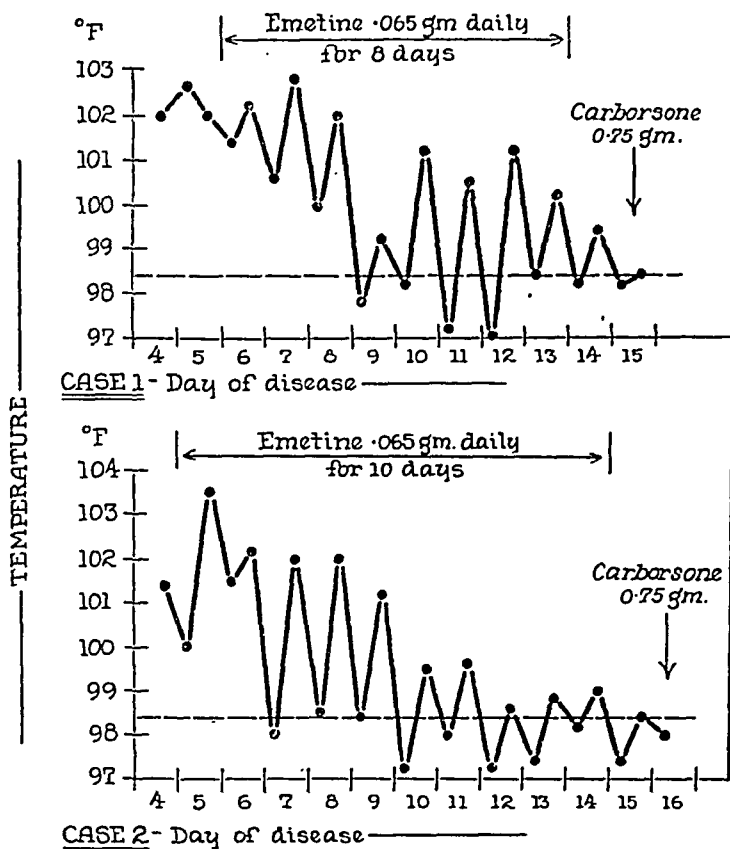


CHART 1. THE EFFECT ON THE TEMPERATURE OF TREATMENT WITH EMETINE IN AMEBIC HEPATITIS

A. Case 1, onset 9 March 1944 with right upper abdominal pain referred to the right shoulder; fever 104° on 10 March; admitted 13 March, acutely ill, temperature 102° . Examination showed marked tenderness and rigidity over the liver, with tenderness on percussion and compression of the lower right thorax, and pain on deep breathing. The chest was clear by physical examination and x-ray. Motion of the right dome of the diaphragm was limited. The leukocyte count was 21,000. The stools were negative for amebae. Emetine 0.64 gm. (H) was administered on 15 March and daily thereafter for 8 doses. Carbarsone 0.25 gm. t.i.d. was then given for 10 days. By 17 March the patient improved subjectively. By 18 March the temperature began to subside. On 22 March it reached normal and remained normal thereafter. He was discharged 4 April with slight tenderness over the liver. He was seen on follow-up more than a year later (14 June 1945), having had no evidence of residual or recurrent amebiasis since discharge.

B. Case 2, onset of dysentery 8 February 1944. Onset of epigastric pain 11 February. On deep breathing pain became sharp and was referred to the left shoulder. Admitted 13 February with temperature of 101° , marked tenderness and rigidity over the liver, pain on compression of the right lower thorax. WBC 19,500 with 59% polymorphonuclears. Stool positive for trophozoites of *E. histolytica*. Emetine 0.64 gm. (H) was administered on 13 February and continued for 10 days. Carbarsone 0.25 gm. t.i.d. was then given for 10 days. On 18 February symptoms had improved. On 19 February the temperature subsided markedly. He became afebrile on 21 February and was discharged the 25th of March with some residual hepatic tenderness.

He was seen on follow-up over a year later (17 June 1945). He had been well for 5 months after discharge. Then he began to have episodes of fairly sharp pain in the right chest below the nipple. The pain was usually of short duration. At present there is slight tenderness over the liver, no rigidity, no fever, no leukocytosis and no diarrhea. Stools are negative. Amebiasis cannot be proved, and definite evidence of hepatitis is lacking.

V. AMEBIC HEPATIC ABSCESS

This complication was demonstrated in only 4 of 523 proved cases of amebiasis in American soldiers. The incidence, 0.76 per cent, is in sharp contrast to that recorded elsewhere. Oschner and De Bakey (2) observed liver abscess in 17.4 per cent of 1333 cases of amebic dysentery. Craig (3) found an incidence of 5 per cent, and Tao (4) 1.8 per cent in large series of cases of amebiasis. Our limited experience with amebic hepatic abscess warrants only brief comment. All of our patients presented the clinical picture, described above, of sudden, severe upper abdominal pain without dysentery but with high fever, marked leukocytosis and prostration. All failed to make a satisfactory recovery after a course of anti-amebic therapy and surgical treatment was considered necessary. In only 1 of our 4 patients were the physical signs sufficiently localized to permit aspiration of the abscess without preliminary laparotomy. In the other 3 aspiration was carried out under direct visualization at the time of laparotomy. In 1 of these 3 surgical drainage of the abscess cavity was also instituted. In no case was more than 100 c.c. of pus obtained. Two patients made a complete recovery, 1 had 3 subsequent recurrences of hepatitis all responding to anti-amebic therapy, but was unable to return to duty. The final patient returned to duty after a prolonged convalescence but several months later still had hepatic tenderness and leukocytosis indicative of residual hepatitis.

In retrospect, it seems probable that these patients would have recovered with more prolonged anti-amebic therapy, thus avoiding surgical treatment. We are inclined to believe, however, that if surgical treatment for small abscesses such as these is considered necessary, it is preferable to aspirate them after preliminary laparotomy, since even under direct visualization their location was not at once apparent. This procedure also minimizes the possibility of overlooking multiple abscesses, the drainage of which is desirable.

VI. "ASYMPTOMATIC" AMEBIASIS

Positive evidence of amebiasis was discovered in 72 individuals who did not consider that they suffered from dysentery. Thirty-three had trophozoites and 39 had cysts of *E. histolytica* in their stools. Examination of the stools had been made for a variety of reasons. Some of the individuals tested were food handlers who were examined monthly. A large proportion were patients with some other illness in whom examination was either carried out as a routine procedure or was prompted by a suggestive past history of dysentery, by the development of mild diarrhea or abdominal discomfort, or by the discovery of eosinophilia, which resulted in a search for intestinal parasites. Symptoms of amebiasis were in no case a primary concern of these individuals, though

they were not entirely asymptomatic, since 38 per cent of the group gave a history of previous attacks of diarrhea or dysentery, 30 per cent were having abdominal symptoms other than diarrhea when seen by us, 25 per cent had abdominal tenderness on palpation, and 11 per cent developed loose stools while in the hospital. These figures are believed to be higher than would have been obtained from a group of well soldiers, and they support the view that amebiasis usually produces symptoms, often mild, but in most instances clearly discernible on close questioning.

DISCUSSION

The conditions of wartime practice in the field usually limited the opportunities for carefully planned hospital and follow-up studies. Detailed clinical investigation was of necessity a secondary consideration except in special circumstances. We are fully aware that our observations of amebiasis were in many respects subject to these limitations. Our present concepts of the disease, although gained from a relatively extensive experience, might well require revision had the opportunity existed for more intensive and prolonged study of our patients. For example, in the administration of emetine we found no evidence of toxicity. It is entirely possible that had it been feasible to make repeated electrocardiograms of all patients receiving the drug some evidence of myocardial damage might have appeared. We can only report that in over 1000 cases no cardiac symptoms or signs developed which suggested this possibility in spite of the fact that the great majority of patients remained ambulatory during treatment.

Our data indicate that both the immediate and late results of treatment were highly satisfactory. In our experience the problem of chronic, recurrent, emetine-resistant amebiasis was practically non-existent. Careful British observers (5-9) take a far less sanguine view, based on experiences in the same theatre of war. The reasons for such divergent results cannot be surely identified. The promptness and thoroughness of the treatment of the initial attack is a factor of recognized importance in avoiding chronicity. The average length of stay in India and Burma was probably greater for British than for American troops, hence they were exposed to greater possibility of reinfection. Further, during the retreat from Burma in 1942, where many British cases originated, the treatment was necessarily delayed and often inadequate. It is probable that larger numbers of British than American troops were subjected to conditions favorable for the development of chronic non-specific post-amebic colitis. Future experience in Veterans Administration hospitals will reveal whether or not the problem of chronic recurrent amebic dysentery is greater than we now believe it to be.

Our experience with amebiasis in a young and healthy segment of the

population has left us with certain outstanding impressions which may be of interest to those who, like ourselves, have heretofore encountered this disease only rarely in civilian practice.

1. *E. histolytica*, whether because of strain differences or variations in the susceptibility of the host, differed tremendously in its pathogenicity. Two individuals might harbor motile trophozoites in the colon, 1 of whom was entirely asymptomatic while the other had a severe, fulminating dysentery. Between these extremes were clinical syndromes of all degrees of severity.

2. In general amebiasis was a disease of the ambulatory patient. The great majority had relatively mild constitutional symptoms and were not confined to bed. This was in sharp contrast to bacillary dysentery which produced rapid prostration as a rule.

3. Of all of the clinical manifestations of amebiasis, acute amebic hepatitis presented the most challenging problems of diagnosis and treatment. This was due primarily to the fact that the syndrome had to be distinguished on clinical grounds alone from a number of surgical conditions which required immediate operative intervention.

4. Proper selection and examination of stools together with proctoscopy were of great importance in facilitating prompt diagnosis and adequate treatment.

5. Present day treatment both in terms of immediate and late results was very satisfactory, though the conditions in which these observations were made did not permit a long-term evaluation of results, which must remain sub judice.

SUMMARY

In an Army general hospital in Assam India over 1000 cases of amebiasis were encountered from April, 1943, to April, 1945. Of these, 382 cases occurring in Americans have been analyzed for this report.

Amebic dysentery was observed in 258 cases. It was manifested by abdominal pain and the frequent passage of loose stools usually containing blood and mucus. The severity of the symptoms varied greatly. In the usual case the onset was relatively insidious, associated with cramp-like abdominal pain and the passage of 5 to 10 stools per day but unaccompanied by severe systemic symptoms. In a small proportion of cases the onset was acute, with high fever, leukocytosis, intense abdominal pain with 20 to 30 bowel movements daily. Whatever the mode of onset positive physical signs usually consisted only of abdominal tenderness, most frequently in the left and right lower abdominal quadrants.

Proctoscopic examination revealed a variety of lesions and was considered very important in facilitating diagnosis and as a guide in therapy.

If care was exercised to select that portion of the stool containing blood and mucus positive laboratory diagnosis could be made on the first examination in

the majority of cases. If 5 examinations were negative further search was usually unavailing.

Amebic dysentery in Assam and Burma had to be differentiated from bacillary dysentery, non-specific diarrhea, the dysentery of malaria, and diarrhea associated with parasitic infestation, notably hookworm disease and strongyloidiasis.

Emetine hydrochloride, given subcutaneously or intramuscularly, in a dose of 0.065 gm. (1 grain) daily for 7 to 10 days, concurrently with carbarsone or vioform by mouth in a dose of 0.250 gm. (4 grains) 3 times daily for 10 days, constituted the standard method of treatment. The results of treatment, both immediate and late, were considered highly satisfactory. A single course of treatment usually rendered the stools ameba free.

The co-existence of amebic and bacillary dysentery was encountered in 8 instances. The clinical picture was usually that of bacillary dysentery. The double infection did not constitute any special problem, did not prolong the period of hospitalization or interfere with the uniformly favorable outcome in both diseases. In 21 per cent patients with the clinical picture of amebic dysentery it was not possible, even after careful study to verify the diagnosis by laboratory methods, hence "clinical" or "probable" amebic dysentery remained a frequent diagnosis.

Amebic hepatitis was encountered in 30 patients. In 15 it was a transitory, clinically unimportant complication of amebic dysentery. In the remainder it produced a dramatic clinical picture, the salient features of which were acute severe upper abdominal pain, usually without dysentery, high fever, leukocytosis, extreme pain on compression of the usually enlarged liver, and elevation of the diaphragm on the affected side. The syndrome had to be distinguished from that produced by perforation of a peptic ulcer, acute calculous cholecystitis, or acute pancreatitis. The favorable response to antiamebic therapy was usually prompt and unmistakable.

Amebic abscess was demonstrated in only 4 patients. In each the presenting clinical picture had been that of severe amebic hepatitis, but the initial clinical response to therapy had been incomplete, prompting surgical treatment. In every instance the abscesses were small and were evacuated by aspiration carried out in 3 instances under direct observation after laparotomy.

"Asymptomatic" amebiasis was encountered in 72 patients. Treatment with carbarsone or vioform was very satisfactory. We were inclined to believe that the amebic infection was probably responsible for mild symptoms which had been disregarded by the patients.

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OBSERVATIONS ON THE METHYLENE BLUE TEST FOR BILE PIGMENT IN URINE

WILLIAM F. LIPP, M.D. AND ALFRED R. LENZNER, M.D.

From the Department of Medicine of the University of Buffalo, and the Buffalo General Hospital, Buffalo, New York

INTRODUCTION

The methylene blue test (1) has been proposed as a simple method for the detection of bilirubin in urine. Most communications record its value in the early diagnosis of infectious hepatitis or in dystrophies due to hepatotoxic agents where it has been reported to become positive before the appearance of clinical icterus. Although the exact mechanism of its action is not understood, some studies suggest that the blending of pigments is more important than a chemical reaction in producing the color change from blue to green which constitutes a positive test. Although there is reason to believe that the test is not specific for bile pigment, practically, in health or disease there are few pigments that will appear in the urine in sufficient concentration to give a misleading positive test. At the present time there does not seem to be a satisfactory method for the detection of small amounts of bilirubin in urine. The so-called "foam" or "shake" test is perhaps most widely used.

Most reports on the use of the methylene blue test stress the infrequency of false positive readings in long series of cases. It was the purpose of this study to explore the possibilities of false negative tests by attempting a correlation between the serum bilirubin and the reading of the methylene blue test. It should be remembered that there are several physiological variables, such as possible variations in the renal threshold, that do not permit a fixed and predictable equilibrium among the serum level of bilirubin, the degree of clinical icterus, and the amount of bile pigment in the urine.

MATERIAL AND METHODS

Simultaneous determinations of serum bilirubin and examinations of urine with methylene blue were made on a group of 175 patients, including a number with jaundice (of both intrahepatic and extrahepatic types) and liver disease without jaundice. Two hundred and eight determinations were made. Specimens were obtained at approximately the same time in the morning, before breakfast. Serum bilirubin values were determined according to a modification of the method of Thannhauser and Anderson (2). The modified methylene blue test was performed according to the technique of Gellis and Stokes (3). The dye, a 0.2 per cent aqueous solution of methylene blue chloride, was added dropwise to 5 cc. of urine. Pipettes were used which delivered 20 drops

of the solution per cubic centimeter. If a green reaction occurred and remained after the addition of 5 drops, the test was considered positive. In a few instances the resulting color was neither blue nor green, but rather aquamarine. Such a result was arbitrarily interpreted as borderline. In the large majority of tests two observers evaluated the color change.

RESULTS

The results of the methylene blue test were as follows:

Positive.....	33 determinations
Borderline	7 determinations
Negative	168 determinations

Positive tests: The majority of cases (29 of the 33) were diseases of the biliary tract producing clinical jaundice (both intrahepatic and extrahepatic). The serum bilirubin values ranged from 1.2 to 19.2 mgs.

In 4 there was no clinical jaundice (1 metastatic carcinoma of the liver, 2 therapeutic malarías, 1 abdominal Hodgkins); and in these the serum bilirubin values ranged from 1.2 to 1.6 mgs.

In the majority of instances (29 of the 33) the "foam" test was also positive. Four negative "foam" tests occurred in cases with a serum bilirubin range of 1.2 to 1.4 mgs.

Thus, in all positive methylene blue tests the level of serum bilirubin was 1.2 mgs. or more.

Borderline tests: There were 7 instances in which the resulting color was described as aquamarine. In 4 of these the serum bilirubin values ranged between 1.2 and 2.0 mgs., and in one it was 1.0 mgs. These 5 cases all had evidence of biliary tract disease: two had clinical icterus. In one case (appendiceal abscess) the serum bilirubin level was 0.2 mgs.; in one (prostatectomy with bloody urine) it was 0.35 mgs.

Thus the production of an aquamarine color usually indicates the presence of bilirubin in urine in excess and a level of serum bilirubin of 1.0 to 2.0 mgs. It should thus be considered a probable positive test.

Negative tests: There were 168 negative tests. In 157 of these the value of the serum bilirubin was below 0.7 mgs., usually in the range of 0.2-0.4 mgs. None of these had clinical icterus or other evidence of biliary tract disease.

In 11 instances, however, the serum bilirubin levels were elevated, ranging between 1.2 and 1.8 mgs. Although negative "foam" tests appeared to confirm the finding with methylene blue, it seems probable that abnormal amounts of bilirubin were present in these specimens. Ten of this group had clinical evidence of biliary tract disease (6 portal cirrhosis, 2 common duct stone, 2 infectious hepatitis) of which 8 were showing clinical icterus when the speci-

mens were obtained. The other was a case of diabetes mellitus with no known reason for the increased amount of bilirubin in the serum.

Thus, in the negative group a false negative reaction occurred in 11 instances (6.5%) either in the presence of clinical icterus and/or increased serum bilirubin, in the range 1.2 to 1.8 mgs.

SUMMARY

1. A positive methylene blue test indicates the presence of an excess of bile pigment in urine.

2. A negative test may occur (6.5%) in the presence of mild degrees of hyperbilirubinemia (1.2–1.8 mgs.) with or without clinical jaundice.

3. A borderline (aquamarine color) test usually suggests a mild excess of bile pigment in urine.

4. The following correlation between serum bilirubin levels and the results of the methylene blue test obtained:

a) Serum bilirubin levels of 2.0 mgs. and above produced a positive test.

b) Serum bilirubin levels of 1.2–1.9 mgs. (33 cases) produced a positive test in 17 cases, a borderline (positive?) test in 5 cases, and a negative test in 11 cases.

c) Serum bilirubin levels of less than 1.0 mgs. (159 cases) produced no positive tests, 2 borderline (positive?) tests, and 157 negative tests.

5. In the majority of instances the results of the methylene blue test paralleled those of the "foam" test.

CONCLUSION

The methylene blue test is a reliable index of the presence of excessive amounts of bile pigment in urine. False negative tests may occur in the presence of mild increases in serum bilirubin, thus impairing its usefulness. If, as reported, the test becomes positive before the appearance of clinical icterus, it might serve as a useful screen in the detection of early cases of infectious hepatitis or of the dystrophies occurring as a result of exposure to certain industrial poisons, when serum bilirubin determinations are not available.

We wish to thank Doctor Roger S. Hubbard for his help in the preparation of this material.

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ORGANIZATION OF THE GASTROINTESTINAL SERVICE IN THE ARMY DURING THE SECOND WORLD WAR: PERSONAL OBSERVATIONS AND IMPRESSIONS*

JOHN L. KANTOR, M.D. COLONEL, MED. RES., U. S. ARMY

As our Second World War effort comes to a close, it becomes apparent that the treatment of gastrointestinal cases in the U. S. Army has been fully in keeping with the developments and requirements of modern medicine. This record is largely due to the farsighted policy of the Surgeon General's Office, which early in 1940 began to plan for the best utilization of professional services in the war-type army hospitals. It is a source of pride to the writer that he was able to participate in the planning of the gastrointestinal sections for these hospitals at that time. Such sections were authorized not only for all general hospitals of 1,000 beds or over, both in the Zone of the Interior and in the various theaters of operations, but were also made available for domestic station hospitals of 800 beds or more. Before the war ended, sections of gastroenterology were operating not only in the field in the numbered general hospitals, but also at home in the named general hospitals (e.g., Lawson General Hospital), the unnamed general hospitals (e.g., U. S. Army General Hospital, Camp Butner, N. C), the regional general hospitals, and the large station hospitals. The status of gastroenterologists received final recognition in the army by the assignment of a Military Occupational Specialist's number 3105, to all qualified officers.

As you may recall, lists of qualified civilian gastroenterologists and gastroscopists were assembled in 1941 and 1942 in the form of four reports by your Committee on Military Preparedness and were made available to the Surgeon General of the Army. Many of the men on these lists actually served as army gastroenterologists, either as chiefs of sections, or as assistants. Some of the members of this association were among this number, to say nothing of those who served in other capacities, such as instructors or administrators, in both the Army and the Navy.

At various times, during his period of active duty in the Second World War, the writer had the privilege of observing the work of sections of gastroenterology not only in his own unit, the 49th General Hospital which functioned in the Asiatic-Pacific Theater, but also in the 51st General Hospital in the same theater, the Tilton General Hospital at Fort Dix, the Fitzsimons General Hospital at Denver, the Borden General Hospital at Chickasha, Oklahoma,

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the Lawson General Hospital at Atlanta, the U. S. Army General Hospital at Camp Butner, N. C., and the Station Hospital, Camp Carson, Colorado.

In all these hospitals the number of gastrointestinal cases generally corresponded to the previously estimated proportion of 10 per cent of all medical admissions. It would have been larger, say 15 to 20 per cent, had all hospitals adopted the policy of admitting their hepatitis and dysentery cases to the sections of gastroenterology instead of to the general medical sections.

The work done by the sections of gastroenterology, as is evident from the reports already published, was professionally of a high order. Gastrosopies were carried out by specially trained officers in a few of the general hospitals. It seems probable that our next important contributions on the clinical significance of gastritis will come from the experience of "military gastroscopists." It may be noted in passing that Dr. Schindler worked under Navy, not Army, auspices on the west coast, and that some of his conclusions have already been published. Proctoscopies were performed routinely; liaison between the gastrointestinal sections and the roentgen and laboratory services was universal, and consultations with the general medical, surgical, and neurological sections were routine.

It is only fair to state that good gastrointestinal work was done not only in the special *sections of gastroenterology* of the larger hospitals, but also in their *general medical sections*, as well as in the evacuation hospitals and the smaller *station and field hospitals nearer the front*. Some publications have already appeared from these sources, and much credit is due to the individual initiative of the authors. Nevertheless it is probably safe to conclude that it was the sections of gastroenterology of the general hospitals that gave the impetus to and set the tone for the special work in this field throughout the army. Not only did they furnish excellent professional care to their patients, but they gave junior officers desirable training in our specialty. Some of these officers were ordered to mobile field units where they undoubtedly put into practice at the front many of the lessons they had learned in the fixed institutions in the rear. In not a few instances the sections of gastroenterology served as training institutions for those aspiring to become specialists in gastroenterology on their return to civilian practice. I have in mind several men whose experience in army gastrointestinal services has been so long and so intensive as to encourage the belief that it will meet some, if not all, of the practical requirements for certification in our own specialty by the American Board of Internal Medicine.

This sketch, prepared in response to a request for a brief statement of personal recollections and impressions, is obviously superficial. For a more complete record of army gastroenterology in the Second World War those interested are referred to the account now being prepared in the Historical Section of the

Surgeon General's Office. However, it is hoped that enough has been said to justify the belief that both as a national body and through the individual contributions of its members, the American Gastroenterological Association has adequately met its war time obligations, and that when the returns are all in we shall be able to contemplate our efforts with reasonable self-approval and satisfaction.

GASTRIC SURGERY: A REVIEW OF THE LITERATURE FOR 1945

SAMUEL F. MARSHALL, M.D.

Department of Surgery

AND

IVAN C. SCHMIDT, M.D.

Fellow in Surgery, The Lahey Clinic, Boston, Massachusetts

The publications dealing with gastric surgery in 1945 reveal progress, with no startling developments. Continuing experiments added to the knowledge of gastric physiology in relation to surgery, and the transthoracic route in attacking certain gastric lesions were used in an ever-increasing number of cases. Further reports on the results of vagotomy were published. Older, more standardized procedures, however, have continued to be the basis of most gastric surgery.

PHYSIOLOGY

Smith et al. (1) studied gastric acidity in 50 apparently normal healthy individuals. They found the variations in normal much greater than those listed in standard textbooks. Values for total acidity ranged from 20 to 90 degrees, and in more than half of the cases total maximal acidity was attained at the end of forty-five minutes. There was considerable variation in the total acidity of individual subjects tested repeatedly at intervals of a few days.

Brown and Rivers (2) tested gastric acidity among men and women suffering from duodenal ulcer by fractional analysis of gastric contents after injection of histamine. They found that male patients had much higher values for free and total acidity than female patients. The values for free and total acidity in males were 90 and 103 degrees, respectively, and the high point reached in an average of fifty minutes, while in females the values were 65 and 80 degrees, and these values reached in thirty minutes. They concluded that the higher and more protracted hyperacidity among the men may help to explain the greater tendency to intractability of duodenal ulcer in males.

Merendino et al. (3) studied the influence of daily intramuscular injections of caffeine alkaloid in beeswax on ulcer genesis in guinea pigs and cats, and found that typical peptic ulcers were produced in 40 per cent. Their experiments suggested that the mechanism of ulcer production with caffeine is related to increased production of free acid. In 73 per cent of human beings tested, 2 cups of black coffee caused a definite stimulating effect on gastric acidity and volume. This was attributed to the caffeine content of the coffee.

Grossman et al. (4) found that the output of pepsin, as well as the concentra-

tion, in response to caffeine is approximately the same as that in response to histamine for the first seventy-minute period, but the caffeine effect is sustained longer than that of histamine. When caffeine and histamine were injected simultaneously, the secretion of pepsin was greater in amount than the sum of the response to the drugs when administered individually.

The effect on gastric secretion of pedicled jejunal grafts in the wall of the stomach was studied by several investigators (5, 6, 7). They found that there was no inhibition of gastric secretory activity by the graft (5), that it did not curb the digestive properties of the gastric juice (6), and that perfusion of the stomach with jejunal washings did not significantly alter the secretory response of gastric acid to histamine in the dog.

GASTROSCOPY

Hardt et al. (8) conducted an analytical survey of 1,132 patients who were both gastroscopied and studied roentgenologically. In their series, gastroscopy was superior to roentgenology in the diagnosis of all types of gastric ulcer, including marginal ulcer. The gastroscopist was correct in 89 per cent of all benign ulcerating lesions; the roentgenologist was correct in 58 per cent. They also found gastroscopy superior in the diagnosis of carcinoma of the stomach. Gastric carcinoma was recognized gastroscopically in 94 per cent, whereas the roentgenologist diagnosed carcinoma in 78 per cent. When combination of the two methods was used 98 per cent of the carcinomas were diagnosed correctly.

Benedict (9) believes, as a result of a study of 245 cases to correlate gastroscopic, roentgenologic and pathologic findings, that gastroscopy is of value in the ulcer-cancer problem and that the most accurate results are obtained when all methods are used cooperatively.

Howard (10) stated that gastroscopy is an adjunct to roentgenography but is less critical than the latter. He believes that the diagnosis of chronic gastritis is interesting but not of great clinical importance.

Mejia and Bolo (11) stated that marginal ulcers situated above the suture line can be diagnosed only by gastroscopy, as a rule, and believe that gastroscopy should be a routine procedure in cases in which symptoms recur after operation for ulcer.

Schindler (12) reported a case in which there was passage of air through the gastric wall during gastroscopy, but no perforation of the stomach could be found at operation three hours later although air was still present in the abdominal cavity. He concluded that the pressure of the instrument had caused a slit-like rupture which closed immediately.

Cardiospasm. Clagett et al. (13) discussed the treatment of cardiospasm, and stated that the great majority of patients suffering from this condition can be treated successfully by hydrostatic dilatation. Approximately 70 per cent

are relieved by one course of treatment. In 30 per cent there is a tendency for the condition to recur at any time, from immediately to twenty-five years later. In 2 to 5 per cent of cases surgical intervention becomes necessary. Their choice of operation is esophagogastrostomy by the transabdominal approach, which resembles the Finney pyloroplasty. They stated that one should not expect regression in size of the esophagus after this procedure.

Foreign bodies. Sarnoff and Sarnoff (14) reported a case in which gastrotomy was performed on a child and a trichobezoar was removed.

Intussusception. Poppel and Herstone (15) reported a case of spontaneous intussusception of the stomach in the absence of a mass. The symptoms were acute continuous epigastric pain, nausea, vomiting and hiccuping. There had been a similar attack six weeks earlier. Roentgen examination revealed that the distal half of the stomach was markedly narrowed; the duodenum was markedly widened as far down as the lower part of the second portion. The widened duodenum acted as the intussusciens, the narrowed stomach the intussusceptum. Spontaneous reduction occurred, but there was a later seizure.

Gastric volvulus. Hamilton (16) discussed gastric volvulus. He gave as etiologic factors obesity, trauma, marked weight loss preceding gastric rotation, and increased intra-abdominal pressure associated with obesity and anomalous development. Some cases are associated with eventration of the diaphragm. He stated that in carefully selected cases it is possible that a surgical procedure may be helpful in restoring the stomach permanently to a normal position, with relief of symptoms.

Gastric schwannoma. Sanguily and Leon Blanco (17) reported a case of schwannoma in a 58-year-old colored woman. The preoperative diagnosis was trichobezoar. The tumor was removed transgastrically through an anterior gastrotomy.

Actinomycotic granuloma. Fuller and Wood (18) reported a case of actinomycotic granuloma of the stomach treated by partial gastrectomy. Fifteen months after operation the patient was in good health and showed no evidence of extension of the disease. The lesion was considered to be primary, and the authors believed it to be the only one on record of cured primary gastric actinomycosis.

PEPTIC ULCER

Incidence and statistics: Udaondo and Nasio (19) studied the occupations of 2557 patients with gastric and duodenal ulcers, and found a higher incidence among professional people than among physical workers. The highest incidence was found in public officials (the survey was conducted in Argentina). Duodenal ulcer was found to be more common in professional people, whereas gastric ulcer was found most often in physical workers.

Petren (20), in a survey of patients with perforating ulcers operated on in Sweden during 1930 to 1943 inclusive, showed that their number was increasing by almost 3 to 5 per cent yearly up to and including the year 1941. In 1942 a sudden increase of 35 per cent occurred and in 1943 the figure was 75 per cent higher than it was in 1940 and 1941. It is difficult to draw any conclusions as to the frequency of ulcers in general from the number of cases of perforated ulcers. Recent observations show that ulcers in men perforate more frequently than in women, and a duodenal ulcer perforates more easily than a gastric ulcer. The author believed that the rapid rise in the number of perforated ulcers in 1942 was attributable to the increase in the total number of persons suffering from ulcer.

Donovan and Santulli (21) reported on 10 cases of gastric and duodenal ulcers in infancy and childhood. Their patients' ages ranged from three months to twelve years. They feel that although gastric and duodenal ulceration is rare in infancy and childhood, the diagnosis would be made more frequently if it were realized that the condition does occur in this age group. They found hemorrhage the chief complication. It occurred in 6 of the 10 cases reported. Perforation and pyloric stenosis resulting from scarring were also observed. Malignant change was not encountered. They consider indications for surgical intervention to be the same for children as for adults: perforation, obstruction, recurrent hemorrhage and intractable pain.

Aaron (22), in a general discussion of inflammatory lesions of the upper gastrointestinal tract, stated that Fordyst St. John examined 2413 patients without symptoms by fluoroscopy and found that 54 had deformed duodenal bulbs, 7 had cardiospasm, 23 had diaphragmatic hernias, 2 of which were large; 2 had carcinomas; 1 had lymphosarcoma and 1 gastric polyp. He believes that roentgenologic examination of the upper gastrointestinal tract may in time attain the same importance as roentgenologic examination of the lungs. He quoted Bird, Lemper and Mayer who collected 243 proved cases of peptic ulcer in children; 111 in children 0 to 7 years of age and 132 in children 7 to 15 years of age. He concluded that children with digestive disturbances should have roentgenograms of the upper gastrointestinal tract to rule out ulcer.

Etiology and pathogenesis: Wangenstein (23) discussed fractures in the etiology of certain ulcers. He stated that hematemesis following fractures is not infrequent, and that ulcers or erosions of the upper gastrointestinal tract can be produced experimentally in animals by fracture or curettement of the bone marrow. Ulceration can also be produced in animals by the intravenous injection of fat. He suggested that the mechanism of production is probably the plugging of end vessels in the mucosa.

Curling's ulcer: Hartman (24) produced experimental third degree burns of 50 to 60 per cent of the body surface of 80 dogs. Fifty animals were treated

by dressings with vaseline or similar preparations, and Curling's ulcer occurred in 32, or 64 per cent. Thirty animals were treated by tanning with tannic acid or other tanning agents. Curling's ulcer occurred in 2, or 6.6 per cent, and in these dressings were of the wet type. He concluded that loss of plasma, autolysis with infection, and acidosis are etiologic factors in Curling's ulcer.

Koch and Fischer (25) discussed theories as to the cause of Curling's ulcer and presented a case of a 68-year-old man who developed symptoms of acute peritonitis twenty-three days after a second and third degree burn of a lower extremity. Autopsy revealed duodenal perforation.

Herbut (26) presented 5 cases of ulceration of the upper gastrointestinal tract following distant operations: right colectomy, laminectomy, drainage of lung abscess, and peritoneoscopy; the causes of the ulcers were not apparent.

Gray (27) stated that experimental work on animals reported by various authors would indicate that direct trauma over the region of the stomach may be followed by acute peptic ulcer. He presented cases in which acute peptic ulcers, perforated gastric ulcers and perforated duodenal ulcers resulted from trauma. Other cases were cited in which preexisting peptic ulcers were aggravated by injury.

Gastric ulcer and cancer: Allen (28) reported that data for a 10-year period at the Massachusetts General Hospital showed 14 per cent of patients who were treated for benign ulcer proved to have carcinoma of the stomach. Often the lesion appeared to diminish in size by roentgenologic examination and gastroscopy. Occasionally such a lesion could not be demonstrated after one month of treatment consisting of bed rest and nonirritating foods. This was possibly due to a decrease in inflammatory reaction. Diagnostic factors of value in distinguishing ulcer and cancer are:

(1) Location of the lesion. Sixty-five per cent of lesions in the prepyloric area within 2 cm. of the pylorus proved to be malignant. Nearly all lesions of the greater curvature and fundus are malignant. Twenty per cent of lesions of the anterior and posterior walls, and 10 per cent of lesions of the lesser curvature and pylorus itself were malignant. Most diagnostic errors were related to the lesser curvature, where 50 per cent of all gastric malignant lesions occur.

(2) Age of the patient and (3) duration of symptoms. If the patient is beyond middle life, and symptoms have been present less than one year, the patient is five times more likely to have cancer than ulcer. If symptoms have persisted five years or more in this age group, the patient is five times more likely to have ulcer than cancer.

(4) Size of the ulcer. Carcinoma was present in 2 lesions less than 1 cm. in diameter. Conversely, enormous benign lesions have been encountered.

(5) Free hydrochloric acid values were the same in both ulcer and ulcer-cancer groups. In cases of proved carcinoma, 60 per cent had no free hydro-

chloric acid. This indicates that the absence of free acid is in favor of carcinoma. The presence of free acid is of little aid in diagnosis.

Pain is often exactly the same in ulcer and cancer.

Palliative surgery is not indicated in gastric ulcer. Four patients treated by gastroenterostomy died of carcinoma. Even experienced surgeons cannot always tell by palpation or appearance whether a lesion is ulcer or cancer.

Prophylaxis: Winkelstein (29) listed as factors in etiology of ulcer: (1) neuroses; (2) heredity; (3) dietetic errors (coffee, condiments, charged water, fats, alcohol); (4) tobacco; (5) physical and mental fatigue; (6) emotional factors; (7) seasonal or periodic recurrence (spring and fall); (8) infections and (9) reflex causes (diseases elsewhere in the body, especially the abdomen). Patients with ulcer in remission should go on therapy during periods of physical and mental stress or fatigue, during and after upper respiratory infections, after surgical procedures elsewhere in the body, and regularly one day each week and for two weeks every few months.

Experimental surgery: Merendino et al. (30) and Kolouch et al. (31) showed experimentally that a short afferent duodenojejunal loop is an important factor in preventing stomal ulcer in dogs.

Lannin (32) studied 12 surgical procedures, and used Code's method of implanting histamine beeswax in the experimental production of ulcer in dogs. As a result of these experiments, satisfactory surgical procedures were found to be: (1) extensive gastric resection in which 75 per cent of the stomach was removed; (2) Finsterer antral exclusion with excision of antral mucosa; (3) fundusectomy plus gastrojejunostomy.

Inconclusive results were obtained in (1) hemigastrectomy; (2) sleeve resection or segmental gastrectomy; (3) Finsterer antral exclusion without excision of antral mucosa. Procedures condemned by these experiments were: (1) gastrojejunostomy; (2) antral resection; (3) antral resection plus total intra-gastric regurgitation (Schmilinsky). The requirements of a satisfactory operation for ulcer appear to be adequate reduction of gastric secretion, extensive resection of the lesser curvature and antral mucosa, and an afferent jejunal loop as short as possible. These criteria are also advanced by Wangenstein (33).

Surgical treatment and statistics: The surgical problems of duodenal and gastric ulcer, together with results and statistics, were presented by several authors (34-43). There was substantial agreement that the treatment of uncomplicated ulcer is a medical problem. Gastroenterostomy was generally condemned. Subtotal or partial gastrectomy was the operation of choice with most authors, most of whom used an antecolic anastomosis of the Hofmeister or Polya type. Mortality ranged from 2 to 9 per cent. Composite figures showed about 90 per cent satisfactory results from subtotal gastrectomy.

Lahey (44) advocated the use of an identifying T-tube in the common bile duct in gastric resection for duodenal ulcer adherent to the bile ducts. By this measure it should be possible to avoid injury to the common duct without recourse to gastroenterostomy or Finsterer operations by exclusion.

Aseptic anastomosis: Pannett (45) described a method of aseptic anastomosis of the stomach to the jejunum using clamps and the cutting diathermy current. He stated that in his cases there was no postoperative hemorrhage and that convalescence was smoother than with open anastomosis. Monteiro (46) also described a method of aseptic gastrojejunal anastomosis between clamps.

Total gastrectomy: Waugh and Fahlung (47) reported 77 cases of total gastrectomy by the abdominal route at the Mayo Clinic from 1917 to 1943. The overall surgical mortality rate was 44.2 per cent. From 1917 to 1939, 33 patients were operated upon with a mortality of 60.6 per cent. From 1940 to 1943, 44 operations were performed, with a mortality of 3.18 per cent. They attribute the lower mortality to experience, postoperative care and chemotherapy. More than half the patients who survived the operation for carcinoma lived two years or more. Two patients operated upon for benign lesions survived the operation for six and eight years, respectively, and are still alive. Jones and Kehm (48) reported 8 patients upon whom total gastrectomy was performed with no mortality; 6 patients had malignant neoplasms and 2 had benign ulcerating lesions. All the patients were living six to eighteen months after the operation. There was no anemia in the 8 cases in spite of no anti-anemic therapy.

Engel (49) reported a case of a patient on whom a total gastrectomy was performed who had postoperative distress because of lack of space in the jejunum to handle a moderate-sized meal. He created a pouch in the loop of jejunum which had been anastomosed to the esophagus after the manner of a Finney pyloroplasty, with complete relief of symptoms.

Arterial ligation: Somervell (50) replaced partial gastrectomy for ulcer with ligation of the arterial supply of the stomach, with immediate good results. The operation consists of tying five of every six small branches from the gastroepiploic arteries on the greater curvature, without too much traction on the stomach. The sheaf of vessels on the lesser curvature is ligated *in toto*. Arteries only are tied, which is said to be more effective than if veins also are tied. In all cases in which the total acid is above 60, gastroenterostomy was carried out in addition to ligation. There is an immediate and considerable drop in acidity. Only one patient in 380 cases developed gastrojejunal ulcer in contrast to 7 cases of recurrent ulceration in a series of 300 patients treated by partial gastrectomy.

Vagotomy: Dragstedt (51, 52) reported on the results of supradiaphragmatic division of the vagus nerve in 39 patients with ulcer. There was one death postoperatively from bronchopneumonia. There were 30 duodenal, 2 gastric and 7 gastrojejunal ulcers. Gastroenterostomy was performed in addition on 8 patients who had pyloric stenosis. In these cases the transabdominal approach was used. Only one patient in this group failed to get striking and persistent relief of symptoms, and in this case there were symptoms of a neurosis. The first group has remained well and without symptoms for two and a half years, with no restriction of diet or medication.

The chief abnormality in ulcer patients is in the secretion of abnormally large amounts of gastric juice in the interval between meals, especially at night when the stomach is empty and there is no obvious stimulant. By animal experimentation it was found that section of the vagi reduced secretion of gastric juice in dogs to one-half or one-fourth the normal level. The data indicate that hypersecretion of gastric juice is neurogenic in origin and should be reduced more in man than in animals by vagotomy.

COMPLICATIONS OF DUODENAL ULCER

Hemorrhage: Cancino (53) studied the circulation of the stomach in cadavers. The main arteries were injected and roentgenograms taken. He concluded that a perfect equilibrium exists between the arterial pressures of the main arteries. Peristaltic contraction facilitates the blood flow rather than causing anemia in that segment.

A grave gastric hemorrhage causes progressive anemia. If the red blood cell count falls to 3,000,000 in the first three hours, the prognosis is grave. Hemoglobin values of 40 to 50 per cent require transfusion, and a pulse rate of 130 to 150 gives a serious prognosis. Conservative measures of treatment consist in an ice bag to the dorsolumbar region to stimulate reflex vasoconstriction, liquids hypodermically rather than intravenously, blood transfusions, vitamin K intravenously, and no food. An internist should treat the patient until the etiology of the hemorrhage is established. Roentgenologic studies convinced Cancino that an efficient hemostasis requires extirpation of the source of the hemorrhage.

Gray and Sharpe (54) reported on 62 patients on whom the Devine exclusion operation was performed for ulcer. While the results in general were poor, the results in a small group of 16 elderly patients with nonobstructing bleeding ulcers were fairly good. Eighty-one per cent of this group had no further trouble. The authors believe that their survival is a good argument in favor of the operation.

Perforation: Graham and Tovee (55) presented 114 cases of perforated ulcer, of which number 111 were operated upon, with a mortality of 6.3 per cent.

Simple closure was performed by tacking either a free or attached omental graft over the defect, making no effort to close the perforation itself. Sulfonamides were used in the abdomen in only 3 cases. They condemn all procedures except simple closure.

Anderson et al. (56) reported on 34 patients treated surgically for perforated ulcer. Simple closure was performed in 32, with a 21.87 per cent mortality. Simple closure plus gastroenterostomy was performed in 2 without fatality. They believe that radical resection may have its place in selected cases in some clinics, but that for the average surgeon simple closure is the operation of choice.

Black and Blackford (57) reported on 93 patients treated surgically for perforated ulcer. The mortality with simple closure was 9 per cent. In 15 cases in which gastroenterostomy was added, the mortality was 27 per cent. Gastric resection was performed on 2 patients without mortality. They believe that the operation should be limited to simple closure in virtually all cases, but that in some cases subtotal resection may be indicated.

Bisgard (58) stated that the available statistical data indicate that subtotal gastric resection can be performed in the presence of diffuse soiling of the peritoneal cavity within twelve hours after the perforation in good risk cases with a lower mortality than that obtained following simple closure with sutures. With few exceptions, radical resection results in permanent cure in contrast to the high incidence of recurrent ulceration following simple closure.

In a few cases primary resection has advantages that make it almost imperative in experienced hands: (a) perforated resectable carcinomas of the stomach; (b) perforated peptic ulcers with simultaneous hemorrhage, and (c) perforated ulcers with fixed pyloric obstruction.

In another group the choice between radical resection and simple closure is debatable but resection is a justified preference in experienced hands: in (a) perforated peptic ulcers with insignificant or only local soiling; (b) recurrent perforations; (c) very early perforations in very young patients who are otherwise in excellent health. In this group the recurrence rate is high, the risk small, and the need for permanent cure very important.

Gastrojejunal ulcer: Tosseland and McDonald (59) reported the pathologic findings and clinical features of 100 cases of gastrojejunal ulcer. According to this study gastrojejunal ulcer is a disease of middle age. Ninety-three were males and 7 females. Pain was the outstanding symptom, present in 86 per cent of cases. The site varied widely. Hemorrhage, in the form of hematemesis and melena, occurred in 32 per cent. Melena alone occurred in 42 per cent. Vomiting occurred in 24 per cent. Eighty-one per cent of the ulcers were on the jejunal side of the anastomosis, 3 per cent on the gastric side, and 3 per cent on the anastomotic line. The site of the other 13 per cent could not be determined. The clinical symptoms were not in proportion to the pathologic

changes. In some cases of mild gastrojejunitis the symptoms were severe, and vice versa.

Obstruction: Brandberg (60) discussed causes of obstruction following gastric resection and gastroenterostomy. There may be gastroenteric atony, which may be mechanical or the result of distention paresis caused by the operation. A short afferent loop may become distended and parietic. Obstruction of a posterior gastroenterostomy is usually caused by abnormal shortness, fibrous thickening or high fat content of the mesocolon, by compression of the stoma.

Obstruction after a few days of satisfactory emptying may be caused by inflammation or adhesions around the stoma. Temporary obstructions may be relieved by repeated gastric lavage or suction associated with parenteral feeding. In rare cases jejunostomy may be necessary. In most cases the obstruction is overcome spontaneously.

Symptoms following resection: Berkman and Heck (61) discussed the unfavorable symptoms following partial gastric resection exclusive of recurrent ulceration. At the present time the most commonly accepted explanation of these symptoms, known as the dumping syndrome, is jejunal distention. Inanition as a result of these symptoms was overcome by a high protein diet, at first of small bulk, then an increase in bulk to the amount of 2500 calories. By this method, without a further increase in bulk, a diet of 3200 calories may be reached, which will insure weight gain without an increase in the severity of postprandial symptoms. A hypochromic macrocytic anemia which developed in some cases failed to respond to the usual treatment for anemia, but the values for hemoglobin improved after the high caloric diet had produced an increase in weight.

Glaessner (62) studied disturbances in sugar metabolism following subtotal gastrectomy. One hundred grams of glucose in 30 per cent solution was administered to each of 14 patients, with resulting hyperglycemia and characteristic clinical signs: nausea, vomiting, headache, abdominal cramps, coma and nystagmus. These symptoms appeared about twenty minutes after administration of the glucose, coincident with hyperglycemia. The attacks could be prevented by insulin. Patients who had had partial gastrectomy with similar postprandial symptoms were instructed to take 5 to 10 units of insulin before meals. In this way attacks were avoided.

Gastrojejunocolic fistula: Ransom (63) reported 18 cases of gastrojejunocolic fistula during the period 1925 to 1944. In the majority of cases a posterior gastroenterostomy had been previously performed. In only 6 cases was there an earlier history of marginal ulcer. A one-stage procedure was employed, a restorative operation in 10 cases, and gastric resection was included in 4 cases. The mortality was 14.3 per cent. Further operation was necessary in 3 cases because of recurrent ulceration. Subtotal gastrectomy was carried out in these with no mortality.

Marshall (64) described a plan for the surgical management of gastrojejuno-colic fistula. In 1935 Lahey and Swinton reported a 63 per cent mortality in 8 cases treated surgically. In 1938 Lahey suggested a two-stage operative procedure to avoid this high risk. Following this, 14 patients were operated upon, with one death, a mortality of 7.1 per cent. Gastrojejunocolic fistula may be prevented by placing the stoma near the base of the mesocolon as far as possible from the colon. Most patients with colonic fistulas are in very poor condition. Malnutrition and extreme alteration in blood chemistry findings make any extensive operation unwise, and for this reason operation is performed in two stages. In the first stage the terminal ileum is divided and an ileocolostomy is performed between the terminal ileum and descending colon. Following this, the contents of the small intestine and right colon empty into the descending colon and cannot reenter the stomach and jejunum. Subsequently, patients gain weight and the diarrhea ceases. Two or three months later the cecum, right colon, transverse colon and fistulous tract are excised, and high subtotal gastrectomy is performed. The postoperative results are uniformly good.

CARCINOMA OF THE STOMACH

Epidemiology and statistics: Dailey and Miller (65) examined 500 normal men 40 years or older by barium meal and fluoroscopy. Three had persistent gastric lesions; one a gastric ulcer, another a suspected polyp, and a third antral gastritis, the last proved by resection. They quoted St. John, Swenson and Harvey who found 3 gastric malignancies in 2,413 men and women. These, however, were not necessarily asymptomatic. Rigler found 17 cancers and 15 polyps in 217 patients with pernicious anemia. Dailey and Miller concluded that mass surveys are not worth while, but people with pernicious anemia should be examined frequently.

Rigler et al. (66) studied pernicious anemia in relation to tumors of the stomach. Their data indicate that an etiologic rather than accidental relationship exists between pernicious anemia and stomach tumors. Two hundred eleven patients were studied and 8 per cent had carcinoma, 7.1 per cent benign polyps. They concluded that routine semi-annual examination of patients with pernicious anemia is a valuable procedure.

Stout (67) found atrophy of gastric mucosa and cyst formation present to a greater degree and in higher percentages in patients with cancer than in patients without cancer. Pollard and Cooper (68) found that hypertrophic gastritis, when localized, may produce a filling defect difficult to distinguish from carcinoma. The symptoms may be indefinite, and a diagnosis in the individual case cannot be made by either gastroscopy or roentgenography alone.

Oppenheim et al. (69) studied anemia in patients with gastric cancer, and

found that it varies widely with respect to the size of the red cells, but in most cases it is normochromic. They believe that the macrocytic and normocytic anemia of these patients is not on the same basis as that of Addisonian pernicious anemia, but probably is related to the associated hepatic insufficiency.

Surgery: Marshall (70) described a technic for subtotal resection of the stomach for carcinoma in which the omentum is removed at its attachment to the transverse colon. Restoration of gastrointestinal continuity is accomplished by a technic based on the Hofmeister method. The mortality rate has been approximately 6 per cent when this method has been employed.

Brunschwig et al. (71) reported a case of carcinoma of the body of the pancreas in which total pancreatectomy, total gastrectomy, duodenectomy, splenectomy, left adrenalectomy and omentumectomy were performed with recovery. The patient died three and a half months later of abdominal carcinomatosis.

Transthoracic resection of the stomach: An increased number of transthoracic resections of the stomach for carcinoma and other lesions of the fundus and lower portion of the esophagus was reported. Sweet (72) reported on 127 patients with carcinoma of the stomach or esophagus with a 25 per cent mortality rate. Sixty-seven per cent recovered without complications; 8 per cent had complications but recovered. Complications included empyema in 8 cases. Since institution of catheter drainage of the left pleural cavity this complication has not been encountered. Mediastinitis occurred in 4 cases, major wound sepsis in 2, acute parotitis in 3, congestive failure as a major contributing cause of death in 6, myocardial infarction in 3, massive pulmonary embolism in 4 cases. Thrombophlebitis of the femoral vein requiring bilateral superficial femoral ligation occurred in 2 cases. Important factors in maintaining a reasonably low morbidity and mortality rate are the preliminary preparation and support postoperatively. Rest, blood transfusions, nourishing diet, vitamins, digitalis, chemotherapy, all contribute to a low mortality. The operation is performed under oxygen-ether intratracheal anesthesia; splenectomy is not performed unless it is necessary. The left chest is routinely drained by catheter, and a Levine tube is left in place just above the anastomosis. After operation, the patients are placed in an oxygen tent and watched carefully for tension pneumothorax, fluid, collapse or pneumonitis or cardiac arrhythmias. Glucose solution, aminogen, vitamins and chemotherapy are employed. Sweet strongly believes that palliative resections, especially in lesions of the lower esophagus, are worth while, even if the patient is relieved of obstruction for only six months to one year.

Griswold (73) described his experiences in dealing with certain lesions of the stomach by the transthoracic route. He stated that the advantage of this approach is better exposure. Among the chief disadvantages are increased

danger from infection and longer operating time. The patient is placed on his right side and the left eighth, ninth or tenth rib is resected from the angle to the costal margin. The phrenic nerve is crushed. The spleen is routinely removed. He reported 3 cases, in 1 of which the cardia was anastomosed to the stump of the stomach; in the others an esophagogastrostomy was carried out.

Bradshaw and O'Neill (74) reported on 56 patients with lesions of the lower esophagus or cardiac end of the stomach operated upon by the transthoracic route. Four had total gastrectomies, with esophagojejunal anastomoses while 52 had a partial gastrectomy with esophagogastrostomy. The operative mortality was 46.6 per cent.

Clark and Adams (75) reported on 5 cases of transthoracic esophagogastrostomy for benign strictures of the lower esophagus, without mortality and with good results.

Gastrostomy: Spivach (76) reviewed the history and methods of gastrostomy and discussed the Spivach tubovalvular gastrostomy in detail. Meyer and Kozoll (77) reviewed 80 cases of carcinoma of the esophagus treated by gastrostomy and found that 43 patients out of the 80 were dead within two months following the operation. They concluded that the procedure of choice is a transthoracic esophageal resection with anastomosis following adequate pre-operative preparation.

Metastatic carcinoma: Lombardi and Parsons (78) reported a case of metastatic involvement of the umbilicus from inoperable carcinoma of the stomach, apparently the thirty-eighth reported in the literature. They believe that such cases are not so rare as the literature indicates, and that more careful examination of the umbilicus in cases of suspected carcinoma of the stomach is indicated.

Survival periods in carcinoma of the stomach: Appleby (79) reported on 684 patients with carcinoma of the stomach; 193 had an exploratory operation and 31 had a resection. Twenty-four patients survived the operation but all were dead at the end of eighteen months. Custer (80) reported somewhat more encouraging figures. In an interval of fourteen years, 141 patients with an established diagnosis of carcinoma of the stomach were submitted to resection. After five years, 27.06 per cent were alive, and 18.75 per cent were alive after eight years. By contrast, a group of 28 in whom the diagnosis of carcinoma of the stomach was established refused operation and the mortality was 100 per cent at the end of three years.

Schwartz (81) presented a case of a patient who had a history of peptic ulcer for nineteen years, with an apparent transition to malignant disease. This patient survived for two and a half years following the demonstration of bone marrow metastases. Lund (82) presented a well-documented case of carcinoma of the stomach treated by resection thirty-five years ago, with the patient still alive and well at the age of 79 years.

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CLINICAL AND PATHOLOGICAL FINDINGS IN PROLONGED HEPATITIS

CHARLES A. FLOOD, M.D., MAJOR, M.C., A.U.S., AND ELLERY M. JAMES, M.D., CAPTAIN, M.C., A.U.S.

INTRODUCTION

During the past two years, opportunity was afforded at the Walter Reed General Hospital to observe a series of patients who were suffering from persistent symptoms and other abnormalities following acute hepatitis. Most of the patients were soldiers who had developed epidemic hepatitis while stationed in various theatres overseas, and not having recovered rapidly they were evacuated to the United States because of the prospect of prolonged hospitalization. The clinical, laboratory and pathological observations on this group form the basis of the present report. In order to assist in determining the degree of hepatic damage which was present and to ascertain whether there were indications of permanent disease of the liver, biopsies were carried out on fifteen of the patients.

In general, the observations indicated that acute hepatitis may be a much more prolonged disease than has been generally recognized. Persistent laboratory and morphological evidence of disease was found many months after the onset of the acute disease. Some instances were encountered, in which persistent or recurrent hepatitis resulted in the development of hepatic cirrhosis.

Prolonged and chronic hepatitis have been described as a sequel of acute epidemic hepatitis. In 1932 Kalk (1) reported a group of patients who suffered from persistent abdominal discomfort and showed evidence of impaired hepatic function following catarrhal jaundice. Soffer and Paulson (2) found that some patients continue to have an abnormal bilirubin excretion test long after subsidence of an attack of catarrhal jaundice. Polack (3) observed a number of patients who experienced recurrent episodes characterized by anorexia, fatigue, weight-loss and jaundice with right upper quadrant tenderness and hepatic enlargement. Barker and his associates (4) reported observations on seventy-six patients with evidence of hepatitis lasting for over three months as manifested by an enlarged and tender liver with intolerance for exercise. On the other hand, residual symptoms following acute hepatitis were attributed by Caravati (5) to psychoneurosis, occurring in individuals in whom the symptoms appear to be on a psychogenic basis following a long organic illness. Others (6, 7, 8) have reported the occurrence of prolonged disability following epidemic or post vaccinal hepatitis.

The reported pathological studies which have been carried out after an attack of epidemic hepatitis have usually indicated a complete restitution to normal. Lucké (9) studied the livers of soldiers who had had acute hepatitis and subsequently died of other causes and found no evidence of persistent disease of the liver. Roholm and Iversen (10) performed biopsies up to fifty-one days after the appearance of jaundice in acute hepatitis. These observers found that the hepatitis is already pronounced in the first week after the clinical onset, and as a rule it subsides within a month after the appearance of the jaundice. In several late cases they noted an increase in connective tissue reaction which was suggestive of hepatitis cirrhosis.

PRESENT STUDY

The present study is based upon 37 patients with hepatitis in whom evidences of disease persisted for over two months after the initial symptoms. An arbitrary dividing line of two months was selected after a detailed study of 40 cases of acute hepatitis revealed that there was complete subjective and objective recovery in all but one patient within a period of two months after the onset.

In addition to routine tests, the laboratory studies included the five mg. per kilo bromsulphalein test, cephalin flocculation test, sedimentation rate and prothrombin time. Many of the patients also were subjected to gastrointestinal x-ray series, gall bladder x-rays and gastric analyses when symptoms persisted.

The technique of liver biopsy was a modification of the procedure described by Iversen, Poul and Roholm (11). Preliminary medication consists of nembutal (0.2 gm.) by mouth, two hours before and morphine sulphate 0.01 gm. hypodermically one half hour before the procedure. Under novocaine anesthesia, a Vim-Silverman needle is inserted through the right ninth intercostal space just anterior to the posterior axillary line. After the needle enters the complementary pleural space, it is thrust inward against the diaphragm. The needle is then advanced quickly through the diaphragm into the liver. The inner component of the needle is then advanced and engages a small column of liver tissue, after which the outer part of the needle is thrust further inward, sealing the liver tissue and the entire apparatus is withdrawn. Worm-like segments of liver tissue are obtained and fixed in formalin for staining with hemotoxylin eosin and in absolute alcohol for staining the glycogen. In our experience this procedure has yielded specimens which are satisfactory for diagnosis in over 90 per cent of trials. After the procedure, the patient experiences pleuritic pain for several hours. Adhesive chest strapping and codeine are used to control pain and the patient is confined to bed for twenty-four hours.

Clinical findings. The acute phase of the hepatitis had subsided in all of the patients in the group at the time of observation. Hospitalization was necessitated by persistent symptoms, hepatic enlargement and tenderness or abnormal tests of hepatic function. With four exceptions, all patients had been considered to have suffered from naturally occurring acute hepatitis. Three of the four remaining patients had had jaundice which was attributable to yellow fever vaccine and one patient had had carbon tetrachloride poisoning. Most cases were first seen by us two to three months after the onset and continued under observation for two to three months. The period of observation was longer in some cases and a few patients were included who were reexamined one to three years after onset. Usually the course of the disease following the acute phase of illness was characterized by continuously persistent symptoms rather than definite relapses. A small group had recurrent episodes of hepatitis separated by intervals of apparent recovery or inactivity of the disease.

Symptoms. The outstanding symptom in this group of patients was abdominal pain or discomfort. This was usually located in the right upper quadrant or in the epigastrium radiating sometimes to the back or to other parts of the abdomen. The discomfort was described as a dull soreness, present during much of the day and aggravated during periods of exertion. Most individuals were unable to participate, at first, in reconditioning exercises because of increased pain. Occasionally the pain was sharp in character and at times it appeared to be related to food intake. Some individuals also had pain in the right lower quadrant, associated with tenderness over the region of the cecum and ascending colon.

Dependent upon degree of activity, some individuals complained of easy fatigability. At times, fatigue was the chief symptom which interfered with the activities of the day. Vague indigestion or nausea might occur after meals, particularly following the ingestion of fatty foods. The appetite was poor at times but most of our patients had recovered the weight which was lost during the acute period of illness. Nervousness and occasional mild diarrhea were complained of at times but these symptoms were infrequent.

In some patients, a subicteric tint of the sclerae was present. The other significant physical findings were limited to the abdomen. Abdominal tenderness was present in about half of the cases, usually located in the right upper quadrant over the liver edge. This was elicited at times with simple palpation or more frequently with deep palpation during inspiration. The liver may extend one to four fingers breadth below the costal margin, and was enlarged in one quarter of the cases. The tip of the spleen was occasionally palpable. Occasionally there was tenderness in the right lower quadrant over the region of the cecum and ascending colon.

Laboratory data. Mild elevation of the icterus index was present in about half of the patients on initial examination, the values ranging from 10 to 22 units. After several weeks of further observation, the icterus index usually fell to within normal limits. In several patients a subclinical bilirubinemia persisted throughout the period of observation. The longest period after onset of jaundice in which some bilirubinemia was found was two years. Occasionally mild recrudescences of jaundice with slight elevation of the icterus index were observed after a period of freedom from jaundice. Bromsulfalein retention was found in the majority of patients on initial examination and varied from 5 to 45 per cent after forty-five minutes. In most instances, the retention was in the neighborhood of 10 to 15 per cent. A prolongation of prothrombin time was also frequently encountered, varying from 26 to 49 seconds in comparison with control values of 18 to 20 seconds. The cephalin flocculation test was occasionally positive. Mild prolongation of sedimentation rate was often found,

TABLE 1
Symptoms in 37 patients with prolonged hepatitis

Abdominal pain or discomfort.....	22
Weakness and fatigue.....	8
Nausea.....	7
Anorexia.....	3
Diarrhea.....	2
Nervousness.....	2
Vomiting.....	1
No symptoms.....	12

but the readings were never high. Other studies frequently carried out included x-rays of gastrointestinal tract, gall bladder and gastric analyses; and these were within normal limits.

CLINICAL COURSE

The clinical picture early in the disease, as recorded in these cases, was not different from that which is usually found in acute hepatitis. Characteristically the onset was with anorexia, nausea and vomiting followed within a few days by the development of jaundice, and hepatic enlargement and tenderness. Some abdominal pain was present in half of the patients during the early phase and usually was located in the right upper quadrant and was mild in degree. Nothing in the early behavior of the disease indicated that the illness was destined to be a protracted one. Most of the patients were not sicker than the average case of acute hepatitis although there were two patients who were seriously ill at the onset. It was of interest that four of the patients presented the picture of acute hepatitis without jaundice during the early period of illness, with only slight subclinical elevation of the icterus index.

The late course of the illness was variable. The majority of patients became asymptomatic within six months after onset, but some continued to complain of abdominal pain. In a number of cases the subjective complaints appeared to be out of proportion to the objective findings but usually some evidence of disturbed hepatic function was found and most patients who had biopsies performed still showed signs of chronic inflammation of the liver.

Twenty-five of the 36 patients were well enough to be recommended for advanced reconditioning within six months after onset. Three patients were separated from the service respectively 15 months, 25 months and 33 months after the onset; two of these patients had chronic hepatitis and one had conversion hysteria following prolonged hepatitis. The remaining patients continued to have residual symptoms from seven months to two years after onset but were considered well enough for light duty. One case described below died three and a half years after onset.

BIOPSY FINDINGS

A comparison of the biopsy findings with the important clinical findings in fifteen cases is shown in table 2. In twelve instances there was evidence of residual periportal inflammation found at intervals varying from two to approximately twenty-five months after the onset of symptoms of hepatitis. Collections of lymphocytes, mononuclear cells and occasional polymorphonuclear leukocytes were present in the periportal areas with at times some evidence of bile duct proliferation. In one case (Case 4) considerable fibrous proliferation and proliferation of bile ducts were found suggesting cirrhosis. In three patients there were no abnormal changes.

In general, this series of biopsies indicated that complete recovery of hepatic lobules is to be expected following acute hepatitis, but that a slowly subsiding chronic periportal inflammatory process may exist for an indeterminate period following the initial episode. The extremely variable and slow recovery toward freedom from symptoms in some cases may be related to the residual inflammatory process demonstrated. However, complete freedom from evidence of inflammation or proliferation of scar tissue is to be expected but only after a highly variable period, in this series varying from seventy-three to five hundred seventy-eight days. One case (Case 4) showing evidence of portal cirrhosis is the exception, and it may be presumed that the biopsy probably represented a localized area of scarring not representative of the liver as a whole.

The following cases are quoted as illustrative:

Case 10. A 29 year old soldier who became ill with anorexia, nausea and vomiting in the European Theatre on February 7, 1945. After two days, he became jaundiced, was hospitalized and treated with bedrest and a high carbohydrate high protein, low fat regime. The icterus index rose to a maximum value of 80 units and frank jaundice

persisted for three months, fluctuating in intensity. He complained of right upper quadrant abdominal pain which radiated to other parts of the abdomen and over the precordial region. His appetite remained poor and he lost 33 pounds in weight. Gradually the jaundice subsided and the pain became less marked.

Three and one half months after onset, he arrived in the Zone of the Interior, still complaining of abdominal pain, lassitude and occasional nausea. He was 17 pounds underweight. The liver was not enlarged but there was moderate right upper quadrant tenderness. The icterus index was 12 units and bromsulfalein test revealed 10 per cent retention at forty-five minutes. Prothrombin time, cephalin flocculation and sedimentation rate were normal. X-rays of the gall bladder and

TABLE 2
Findings in fifteen cases of residual hepatitis

	APPROX. NO. OF DAYS AFTER ONSET	LIVER EN- LARGEMENT	LIVER TEN- DERNESS	SPLENIC EN- LARGEMENT	ICTERUS INDEX	BROMSUL- FALEIN RETENTION	BIOPSY FINDINGS
							Subsiding chronic inflam- mation
1	73	0	+	0	10		++
2	77	2 fb.	+	0	10	5%	+
3	83	0	+	0	12	20%	++
4	90	3 fb.	0	0	5	45%	+++
5	99	1 fb.	0	0	10		++
6	103	0	0	0	7.5	0%	++
7	107	0	0	0	12	10%	++
8	116	1 fb.	+	0	7	20%	+
9	153	0	0	0	10	10%	+
10	167	0	+	+	12	10%	++
11	181	2 fb.	+	0	17.5	30%	0
12	316	0	+	+	20	0%	0
13	318	0	+	0	5	0%	++
14	578	0	0	0	15	5%	0
15	761	2 fb.	+	0	7	0%	++

upper gastrointestinal tract were normal. A needle biopsy of the liver on July 17th, 1945, showed subsiding chronic inflammation around the portal spaces.

During the first month after return to the United States, icterus index and bromsulfalein tests became normal, but the patient continued to have intermittent right upper and lower abdominal pain, aggravated during exertion. The next two months were spent on convalescent sick leave during which time he improved symptomatically. Nine months after onset he felt fairly well but exercise tolerance was estimated at only about sixty per cent of normal.

This patient showed evidence of prolonged hepatitis. The clinical evidence of liver damage was slight but abdominal pain was a prominent symptom. Biopsy of the liver was done five and a half months after onset and revealed a moderate degree of subsiding periportal inflammation (fig. 1).

Case 4. A 34 year old soldier was hospitalized in New Guinea in June 1944 because

of anorexia and epigastric pain of several days duration. Examination revealed a questionable icteric tint of the sclera. The liver was enlarged three fingers breadth below the costal margin. There was a faint trace of bile in the urine and the icterus index was 21 units; rising to 29 units. After two weeks the abdomen became distended and it was noted that he had some pretibial edema and shifting dullness was present in the abdomen. Following this, he had a profuse hematemesis and the red blood count dropped to 2,800,000 with hemoglobin 71%. The white count and blood platelets were normal. A transfusion was required. Paracentesis three weeks after admission yielded straw colored fluid with specific gravity 1010, 4-plus albumin and 52 white cells per cubic millimeter, with 90% lymphocytes. During this period there was a slight fever up to 100°. After one month, the patient improved and three months after onset he arrived in the United States. At that time the edema and ascites had disappeared completely and he felt well except for some indigestion and epigastric discomfort. The liver was enlarged three fingers breadth below the costal margin. Bromsulfalein test revealed 45 per cent retention. A biopsy of the liver revealed subsiding periportal inflammation with considerable fibrous proliferation and proliferation of bile ducts, suggesting cirrhosis (fig. 2). Under observation, the patient became asymptomatic but some hepatic enlargement persisted when last examined six months after onset.

This case is illustrative of severe hepatitis with subclinical jaundice at the onset, followed by portal decompensation. The subsequent course was one of continued improvement and six months after onset, the patient was considered well enough for light duty.

Case 15. A 27 year old nurse suffered from an attack of acute hepatitis in May 1942. She had received yellow fever vaccine in December 1941 which was presumably the source of infection. The onset of illness was with fever, rising to 103°, followed by intense jaundice, itching and clay colored stools. The jaundice gradually subsided but during convalescence there was marked fatigability and right upper quadrant soreness. After three and a half months, she was returned to duty. During the ensuing two years, she was hospitalized on three occasions because of persistent symptoms including chronic fatigue, aching sensations in the right upper quadrant, anorexia and slight low grade elevations of temperature varying from 99.2 to 99.6 by mouth. Repeated examinations usually revealed a tender palpable liver extending two fingers breadth below the costal margin. The cephalin flocculation test was intermittently positive while the bromsulfalein test was normal. A biopsy of the liver in June 1944 revealed a moderate degree of periportal inflammation with slight periportal fibrosis. The patient was separated from the service because of physical disability.

This patient is an example of extremely prolonged hepatitis lasting for over two years, where the disease followed and was presumably due to yellow fever vaccine. The principal manifestations were chronic fatigue, enlargement and tenderness of the liver and some histological changes demonstrated in the biopsy of the liver (fig. 3).

Case 16. A 50 year old officer was well until August 1942. At that time, about

1



2



3

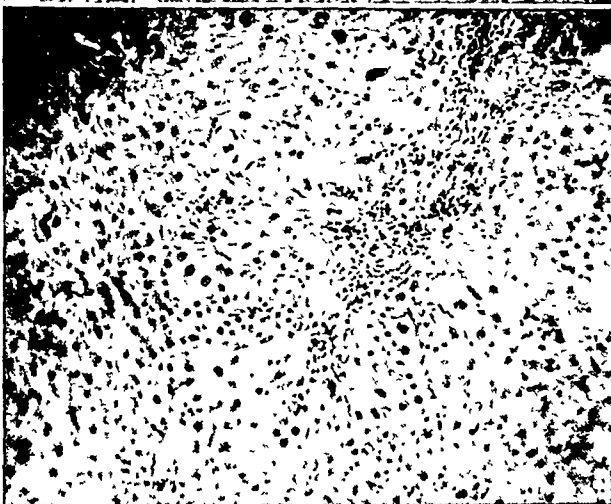


FIG. 1. BIOPSY OF LIVER IN CASE 10 REVEALING A MODERATE AMOUNT OF SUBSIDING PERIPORTAL INFLAMMATION FIVE AND A HALF MONTHS AFTER ONSET OF HEPATITIS

FIG. 2. BIOPSY OF LIVER IN CASE 4 SHOWING CONSIDERABLE FIBROUS PROLIFERATION AND PROLIFERATION OF BILE DUCTS ABOUT FIVE MONTHS AFTER ONSET OF HEPATITIS

FIG. 3. BIOPSY OF LIVER IN CASE 15 REVEALING SLIGHT PERIPORTAL FIBROSIS OVER 2 YEARS AFTER ONSET OF ACUTE HEPATITIS

four months after receiving yellow fever vaccine, he began to feel somewhat below par and on one occasion his eyes were questionably jaundiced. He began to notice swelling of both ankles coming on during the day and subsiding overnight. He also developed very mild abdominal discomfort, associated with slight nausea. He was hospitalized in July 1943 because of these symptoms and improved. After discharge from the hospital, the symptoms gradually recurred. His appetite became poor but weight was maintained. There was increasing fatigability and weakness.

Examination in October 1945, about three years after onset of symptoms revealed a dusky pigmentation of the face and body. There were a number of spider angiomas. The liver was percussed at the costal margin and there was moderate pitting edema of the legs. The icterus index was within normal limits but the bromsulfalein test disclosed a 100 per cent retention. During the next three months, the patient steadily became worse, developed ascites and finally died with hepatic insufficiency. Autopsy disclosed marked cirrhosis of the liver.

This case is an example of cirrhosis of the liver terminating fatally about three years after the clinical onset. The fact that the onset took place shortly after yellow fever vaccine raises the question of a possible relationship. In view of the rarity of such an occurrence, the relationship remains conjectural.

DISCUSSION

Most of the patients in this group presented definite evidence of persistent disease of the liver, continuing for many months after the original onset of acute hepatitis. These findings are in accord with the reports of Kalk, Soffer and Paulson, Barker and others, who reported series of cases of protracted liver disease following acute hepatitis. The principal positive findings in our series were enlargement and tenderness of the liver, slight elevation of the icterus index, retention of bromsulfalein and histological changes in the liver demonstrated by punch biopsy. Less frequently an elevation of sedimentation rate, prolonged prothrombin time or positive cephalin flocculation test indicated persistent disease.

Hepatitis may persist for over two years and frequently lasts for six months. Except for one patient in this series who died of cirrhosis of the liver over three years after onset, the longest interval at which persistent liver damage was found was twenty-five months. The general trend however appeared to be in the direction of recovery within one year. Under observation, abdominal distress usually disappeared, liver function tests returned to normal and while biopsy findings showed some periportal inflammation, there was usually nothing to suggest the onset of cirrhosis.

The problem of the relationship of prolonged hepatitis to cirrhosis of the liver is an unsettled one. Our studies indicate that complete recovery is to be expected following prolonged hepatitis. Over a period of time, there was a slow recovery with disappearance of symptoms and histologically the persistent

changes in the liver were not marked in degree. It is felt that cases of cirrhosis such as Case 16 which may have been a sequel of acute hepatitis, should be interpreted with caution because of the rarity of frank cirrhosis following acute hepatitis. Barker and his colleagues observed a few patients with chronic hepatitis with ascites and spider naevi, some of whom improved and some who developed fatal liver failure, and concluded that cirrhosis of the liver following chronic hepatitis is probably rare.

Two of our cases appeared to fall into the group which has been described by Soffer and Paulson and others (2, 12) who have a persistent or intermittent bilirubinemia following acute hepatitis and lasting for years. These patients were found to have a normal histological appearance of the liver and other liver function tests were within normal limits.

SUMMARY

1. A series of cases of prolonged hepatitis is described in whom evidences of persistent liver disease lasted for six to twenty-five months.

2. The principal positive findings are enlargement and tenderness of the liver, slight elevation of the icterus index and bromsulfalein retention. Biopsy of the liver usually reveals subsiding chronic periportal inflammation.

3. In prolonged hepatitis, complete recovery is to be expected but only after a variable period, in this series varying from seventy-three to five hundred seventy-eight days.

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LAENNEC'S CIRRHOSIS: THE EFFECT OF THERAPY IN INCREASING LIFE EXPECTANCY

STOCKTON KIMBALL, M.D. AND WILLIAM A. C. CHAPPLE, M.D.

The University of Buffalo School of Medicine, Buffalo, N. Y. and the E. J. Meyer Memorial Hospital, Buffalo, N. Y.

INTRODUCTION

Cirrhosis of the liver occurring in chronic alcoholics is common in a big city hospital. The introduction of the Patek regimen has extended the life expectancy of these patients by several years. By way of evidence of this, we are presenting an analysis of the effect of treatment of patients with decompensated alcoholic cirrhosis in the general ward service of a city hospital during two five-year periods, 1936-40 and 1941-45. The 1936-40 group is labelled A, the 1941-45 group, B. An attempt was made to study all of the charts filed in the record room under the diagnosis of cirrhosis of the liver. This was impossible in the earlier group labelled A, since the charts are being microfilmed and were not all available for study. 160 successive unselected charts from this period were studied and compared with 200 successive unselected charts from the later five-year period. In the first five-year period, Group A, our information is derived entirely from the charts. One of us, Dr. William Chapple, has seen most of the patients in the second five-year period, Group B, and has done most of the work for this paper.

OBSERVATIONS

In an attempt to minimize error we have excluded from our study all except those who manifested clinical evidence of hepatic decompensation. As evidence of decompensated cirrhosis we accepted the following: ascites, splenomegaly of marked degree, esophageal varices, and ankle edema.

Jaundice was not included as a criterion because we believe it to be a manifestation of active disease in the liver cells often transitory in nature, rather than a terminal result of cirrhosis. Although Laennec's cirrhosis and cardiac decompensation may often coexist, we have excluded from consideration all cases manifesting evidence of cardiac decompensation so as to avoid confusion concerning the nature of the ascites and ankle edema. We have excluded consideration also of those patients in whom Laennec's cirrhosis was demonstrated at autopsy but did not give enough clinical evidence so that the patients could receive therapy directed toward the relief of their cirrhosis.

Out of 160 patients in Group A, the first five-year period, 57 have been included for analysis, and out of 200 patients in Group B, the second five-year

period, 86 have been included for analysis of patients demonstrating decompensated cirrhosis.

In Group A, 36 of the 57 patients, or 65%, and in Group B, 79 of the 86 patients, or 92%, were confirmed and recurring chronic alcoholics (table 2).

In Group A, 5 or 9% and in Group B, 35 or 41% were described on the charts as showing clear cut evidence of vitamin deficiency. It is probable that the difference in the two groups represents a difference in observation and recording rather than a true difference in incidence. The deficiencies noted included bleeding tendencies such as purpura or bleeding gums, cheilosis, atrophic, red

TABLE 1
Comparative study of 5 year periods

	A	B
Alcoholics		
Large livers.....	42	67
Alcoholics and cardiac cirrhosis.....	42	22
Diagnosis at autopsy only.....	19	25
Decompensated cirrhosis.....	57	86
	160	200

TABLE 2
Decompensated cirrhosis

	A		B	
	number	per cent	number	per cent
Alcoholics.....	36	65	79	92
Deficiencies.....	5	9	35	41
Prothrombin deficiencies.....	2	4	16	19
Low Protein (total).....			23	27
Total.....	57	100	86	100

or purple tongue, pellagra, peripheral neuritis and combinations of these such as tongue plus neuritis, tongue plus cheilosis, tongue plus cheilosis plus neuritis.

Among physical findings (table 3) the liver was described as palpable or enlarged in 32% of group A and 87% of group B; the spleen as palpable in 12% of group A and 11% of group B. How reliable is the description of enlargement of the liver in cirrhosis is questionable. The organ is so much increased in firmness that, even though the liver may actually be reduced in size, its edge is often felt below the costal margin on deep inspiration. Spider angiomas were described on the chart in 2% of group A and in 39% in group B, a description certainly below the actual incidence. Ascites was noted in 82%

of group A and 79% in group B and esophageal varices were demonstrated by X-ray or by gross hematemesis or melena in 23% of group A and 29% of group B. In this regard it is of interest to note that 64% of patients in group B, as compared with 15% in group A, were still living 1-5 years after the demonstration of the presence of esophageal varices.

Jaundice was present during hospitalization in 40% (23 cases) of Group A and 80% (69 cases) of Group B. Despite the greatly increased incidence of jaundice in the second 5-year period, the percentage of jaundice which first

TABLE 3
Physical findings

PHYS. EXAM.	A		B	
	57	%	86	%
Total.....				
Large liver.....	18	32	75	87
Large Spleen.....	7	12	16	11
Spiders on chest wall.....	1	2	33	39
Ascites.....	47	82	67	79
Esophageal varices.....	13	23	25	29
(Deaths in varix group).....	11	85	9	36
Jaundice.....	23	40	69	80
(Terminal only).....	16	69	23	33

TABLE 4
Therapy

	DIET			
	CHO	P	F	Cal.
Group A	400	70	90	2700
	500	60	20	2500
Group B	350	150	60	2550
		(250)		(2950)
		Plasma		

appeared as a part of the terminal picture was only 33% in the second 5-year period, as compared with 69% in the first 5-year period. This suggests an incidence of recovery from active liver disease greater in the second than in the first 5-year period.

TREATMENT

In the first period the diet prescribed was a 2700 calorie "house diet": Carbohydrate 400, protein 70, fat 90; or a 2500 calorie, so called "high carbohydrate, low fat diet" containing carbohydrate 500, protein 60, fat 20. The

standard diet in the second 5-year period contained 150 to 250 grams of protein, 350 grams of carbohydrate and 60 grams of fat. Intravenous plasma was employed occasionally.

Extra vitamins were not added in the first 5-year period. In the second period the vitamins added routinely were: brewers yeast, 30 gm. t.i.d., thiamine chloride 10 mg. t.i.d., orange juice, 200 cc. t.i.d., crude liver extract, 3 cc. intramuscularly daily. For special indications nicotinic acid, riboflavin, vitamin K, or ascorbic acid were added.

Further treatment consisted of withdrawal of alcohol during hospitalization, salyrgan and abdominal and thoracic paracentesis when indicated, and omentopexy in selected cases.

TABLE 5
Average Length of Total Observation per Case

	<i>months</i>
Group A.....	10.8
Group B.....	21.0

TABLE 6
Vital statistics—at end of 5 year period

	A		B	
	<i>number</i>	<i>per cent</i>	<i>number</i>	<i>per cent</i>
Dead.....	46	80	48	55
Living.....	2	4	29	34
Unknown.....	9	16	9	11
Total.....	57	100	86	100

Surgical omentopexy was performed three times in Group A with good results in one case and five times in Group B with good results in three. In addition there was one proven spontaneous omentopexy in Group B with complete relief of the ascites.

RESULTS

The results of therapy in Groups A and B are indicated by the death rate (table 6)—46 deaths in Group A, or 80%; 48 deaths in Group B, or 55%. At the end of the 5-year period two patients were known to be living in Group A and 29 in Group B.

The results indicated by the above death rates compare with the average duration of symptoms recorded in table 5. From the onset of hepatic decompensation in Group A to the time of death averaged 10 months for the

group, or less than one year. From the onset of hepatic decompensation in Group B to the time of death or to survival at the end of the 5-year period averaged 40 months, or 3.3 years. Included in this group are 3 patients who showed evidence of decompensation dating back more than 10 years before their first hospitalization, which occurred during the second 5-year period. To overcome the effect on our statistics of these three extraordinary cases, we have averaged the length of time in group B from the first hospitalization for cirrhosis to death or survival at the end of the 5-year period. This figure was found to be 21 months, or twice the average length of total survival of the patients in Group A after the onset of their symptoms.

The chief causes of death in both groups A and B (table 7) were intercurrent infection,—chiefly pneumonia, cholemia, ruptured esophageal varix and emaciation. Since the actual number of deaths in the two groups, 46 and 48

TABLE 7

CAUSE OF DEATH	A	B
Infection..... (chiefly pneumonia)	13	16
*Cholemia.....	10	15
Esophageal varyx.....	11	9
*Emaciation.....	7	3
Carcinoma liver.....	1	1
Foot amputation.....	1	1
DTs.....	1	1
Suicide.....	2	1
Undetermined.....		2
Total.....	46	48

* indicates significant variations in the two groups

respectively, was practically identical, it will be noted that the only difference in causes of death between the two groups lies in an increase in cholemia in Group A, possibly associated with the increase in incidence of jaundice, and the decrease in death from emaciation, doubtless the result of improved nutrition. The chief difference between the two groups is in the *number*, not in the *nature* of the deaths.

SUMMARY

Out of a total number of 143 cases of decompensated cirrhosis analyzed, the death rate in the second 5-year group after the institution of high protein, high vitamin therapy was found to be $\frac{3}{4}$ that in the first 5-year group. The survival time of patients in the second 5-year group was found to be from 2 to 4 times that of patients in the first 5-year group.

On the basis of the work of Patek, Whipple, Ravdin, Snell, Morrison, Hoagland and others, we feel justified in concluding that this improved clinical result is attributable to improved therapy. Snell has noted that this response to therapy is more striking in alcoholic than in non-alcoholic cirrhosis. By earlier institution of therapy, at least in cirrhosis in occurring chronic alcoholic patients, hepatic decompensation can be delayed and perhaps avoided entirely. The purpose of this paper is to promote this point of view.

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ANION EXCHANGE RESIN AND PEPTIC ULCER PAIN

MARY M. SPEARS, M.D., F.A.C.P., AND MILDRED C. J. PFEIFFER, M.D.*

From the Department of Gastro-enterology and Proctology of The Woman's Medical College of Pennsylvania

INTRODUCTION

While there is lack of universal agreement concerning the cause of "peptic" ulceration and the pain often associated with it, nevertheless, the etiologic role of pepsin and hydrochloric acid has been emphasized (1), and much of present day therapy has been directed toward the inactivation of the free hydrochloric acid in the gastric contents.

"Typical" ulcer pain occurs rhythmically from one-half to one and one-half hours after eating (2). Many antacids have been used to neutralize or adsorb the free acid and thereby relieve the pain, but each has certain disadvantages (3). In the last year, resins have been considered as antacids and their clinical study has been suggested (4, 5).

The advantages of anion exchange resins when used as antacids have been found to be: 1., Greater speed of action; 2., Greater neutralizing power when used in practical application; 3., Complete inhibition of peptic activity; 4., Absence of phosphate ion removal; 5., Lack of acid rebound; 6., Absence of constipating effect; 7., No chloride removal (5).

It would seem desirable, then, to endeavor to determine the degree of usefulness possessed by such resins in treating human disease, particularly peptic ulceration.

The primary objective in this study was the effect of an anion exchange resin on peptic ulcer pain.

METHOD

Material. The anion exchange resin used was Amberlite IR-4, or, as it is now known, Resinat (200 mesh). It is a polyethylene polyamine methylene substituted resin of diphenylol dimethyl methane and formaldehyde in basic form. Amber, finely granular, of slightly bitter taste and faintly ammoniacal odor, it is insoluble in water, but capable of reducing the hydrogen ion concentration of gastric juice in vivo and in vitro (4, 5), as well as inactivating irreversibly pepsin. In an alkaline medium,

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The Resinat (200 mesh) was furnished by the Medical Research Department of The National Drug Company, Philadelphia, Pa.

as in the small intestine, the original resin is regenerated, the hydrogen ion being exchanged for another cation.

According to Martin (6), and from the work of Segal et al (4) on the toxicity of Amberlite IR-4 in rats, it was considered safe to use in almost any quantity in humans.

Originally, three preparations were provided: (1) Ten per cent suspension (with sweetening and flavoring agents and a preservative); (2) 0.25 gram of the dry powdered resin in a moderately slowly dissolving gelatin capsule; (3) dry resin powder in bulk form, one level teaspoonful averaging 1.4 grams and one level tablespoonful averaging 3.2 grams, respectively, in weight. The suspension was discarded early in the course of the study because it was inconvenient for the patient and it did not seem suitable for investigational purposes. The preparations supplied were not applicable to intra-gastric instillation through the average gastric tube.

Clinical Grouping. Individuals who participated in the investigation fell into 1, 2, or 3 of 4 groups:

Group I. An Ewald meal (tea and soda crackers) was given in the morning to 25 fasting adult patients, and specimens were withdrawn as in a routine fractional analysis. At the completion of the test, the tube remained in situ, and the patient was given a certain amount of the resin in sufficient tap water to permit swallowing. Samples were then withdrawn at specified intervals, free and total acid content determined, and the amount of resin sediment noted.

Most of the patients constituting this group had peptic ulcerations but some of them had a gastric analysis done for other reasons.

The purpose of this diversion was to determine, if possible, by this crude method, an approximate dose of resin which could be expected to reduce the free hydrochloric acid to zero and to maintain it at that level for at least one hour.

Group II. From June 1945 through September 1946, thirty patients having peptic ulcers with pain constituted this main experimental group. Of these, 25 had a long history, while in 5 the duration of the ulcer was relatively short. All were studied as completely as possible, and all had roentgenological evidence of ulceration, but in 4 cases, difference of medical opinion resulted in classifying these individuals as probable active ulcer patients. Prepyloric and duodenal ulcers were present in one patient; esophageal and duodenal ulcers co-existed in another patient; 26 others had duodenal ulcers; a gastric ulcer was diagnosed in one case; and one man had multiple marginal ulcers.

Four patients were confined to bed at the beginning of treatment. Twenty-six patients were ambulatory and employed in work which involved irregular sleeping and eating hours, together with occasional occupational threats to life (policemen, firemen, guards).

The weight and general nutritional status was average for age and sex, or only slightly below normal.

There were 29 males, 1 female; 28 white persons, 2 colored. The age ranged from 30 to 81 years, the average being 46 years. Direct observation time while using the resin ranged from 15 months to about one week in 4 instances (as in the massive

hemorrhage patient who died following surgical intervention; the complete failure, and 2 who improved so rapidly that they did not wish to report to the Clinic). The average observation time was 5 months. Nine patients were observed for one year or longer.

These patients were given the resin in amounts which at first were on a trial and error basis, and which later were administered according to individual need. Dosage varied between 0.25 gram (1 capsule) after each meal and before bedtime to approximately 6.4 grams (2 level tablespoonfuls) every hour, taken with tap water.

Aside from restrictions on alcohol, tobacco and coarse or highly seasoned food, no

TABLE 1
Composition of patients in Group II

Age.....	30 to 81 Years
Average.....	46 Years
Sex.....	29 Male
	1 Female
Race.....	28 White
	2 Negro
Ambulatory.....	26 Patients
Bed.....	4 Patients
Acute ulcers.....	5 Patients
Chronic ulcers.....	25 Patients
Ulcer site.....	26 Duodenal
	1 Gastric
	1 Prepyloric-duodenal
	1 Esophageal-duodenal
	1 Multiple marginal
"Simple" ulcers.....	21 Patients
Ulcers with complications.....	9 Patients
Observation time.....	1 Week to 15 months
Average.....	5 Months
Amount of Resin Administered in Divided Doses per 24 Hours	0.5 to 102 grams
Average.....	24 Grams

major dietary restrictions were imposed. Meals were to be bland, eaten three times a day, and as regularly as possible.

No other medication was used except as incidental need arose.

Group III. Twenty-three patients having disease entities other than peptic ulcer to account for abdominal pain (gastritis, hyperchlorhydria, carcinoma, sarcoma, allergy, spasm, renal or gall bladder disease and undiagnosed disease), were also given resin in varying doses, according to the plan used in Group II. The purpose of this procedure was to estimate any non-specific effect that the resin might have on pain.

Group IV. Group II and III patients and 3 individuals with bleeding peptic ulcers without pain were combined to form this group of 56 which represents all indi-

viduals who have been exposed to the resin and who have been observed for obvious subjective or objective side effects of the antacid. Twelve patients were observed for one year or longer.

Because the main purpose was not to study toxic effects as such, each person was not periodically subjected to a routine blood count, urinalysis, stool examination (gross and for occult blood), sedimentation rate and a gastric analysis; but as many as possible were so studied.

RESULTS

Group I. Owing to the great variation, even at different times in the same individual, no clear-cut results of administering resin with a gastric tube in situ can be described. There seemed to be a reduction in free acidity even with as little as 0.25 gram, but the duration of such reductions was a matter of 5 to 10 minutes. In certain cases there seemed to be a subsequent transient elevation in free and total acidity in about 15 minutes, which may be considered not typical of acid rebound. It was not until approximately 6.4 grams were given in at least 2 consecutive one-half hour doses, that the free acid titration value was consistently reduced to zero for an hour or longer. The value was lower in those cases in which resin was present in the aspirated specimens than in those having no such precipitate.

Pain, when present during the procedure, was relieved instantly with 0.25 gram as well as 6.4 grams.

Group II. Of 30 patients with ulcer pain, all but one indicated relief of pain. The failure was in one of the first patients to be treated, an 81 year old colored man, who had marked hypersecretion, regurgitation and vomiting. Given a 0.25 gram capsule every hour, he probably had very little contact in his stomach with the resin.

Relief of pain ensued in most cases immediately, especially if the loose powder were taken, and often there was no recurrence. When the capsules were used, pain relief occurred usually within 5 and 10 minutes. Night doses were rarely required, especially if a bedtime dose was taken.

The patient with marginal ulcers, who was in bed with severe pain, was ambulatory in 2 days on a schedule of one capsule every hour, day and night. Patients who had had ulcer recurrences over many years, claimed that the resin was most effective, and returned for additional supplies because they did not want the pain to recur. However, in other instances, relief seemed so complete to the patient that he considered himself cured, and did not wish to return for further observation.

The usually immediate control of pain, however, did not guarantee healing, nor prevent recurrences and complications in 9 cases. One patient with a long

standing duodenal ulcer was symptom-free on 0.5 gram (2 capsules) every one hour, and remained on this schedule 7 months, at which time he developed pain due to perforation and walled-off peritonitis.

Another patient with duodenal ulcer with penetration into the pancreas proven at operation, was symptomless on 0.25 to 0.5 gram (1 to 2 capsules) after meals and 2 grams (8 capsules) at night. He continued on this dosage and was comfortable until 7 months later, when, after dietary and living irregularities, he no longer was free of pain at all times. He was given approximately 3 grams of the powdered resin every hour. He was comfortable until evening, when additional resin failed to relieve him. A subtotal gastric resection and excision of the penetrating ulcer gave relief.

Two massive hemorrhages in close succession and necessitating surgery, followed relief of pain in a 31 year old man, given 0.5 gram (2 capsules) every hour day and night. On the other hand, 2 men who had had bleeding ulcers but no pain have taken 0.25 gram (1 capsule) 4 times a day for over 1 year without, as yet, bleeding.

The 45 year old male with marginal ulcers had a recurrence of pain some months after discharge from the hospital. He had not been "maintained" on resin therapy.

Intensive psychotherapy was necessary to help control a 37 year old man who resorted to the resin off and on as the spirit moved him, for intermittent pain, and who was difficult to maintain on any kind of regimen.

While no attempt was made for the purpose of this report to determine healing time as related to resin therapy, nevertheless, some ulcers did heal, as proven at the time of a laparotomy or by roentgen examination, and some retained roentgen evidence of activity while on resin treatment but produced no symptoms.

The amount of resin ingested did not seem to bear a direct relationship to pain relief. As little as 0.25 gram (1 capsule) could bring about ease within 5 minutes, whereas approximately 6.4 grams also produced relief almost immediately. Two tablespoonfuls (about 6.4 grams) every hour was the largest amount most patients could take because of taste, gagging, or fullness. Dosage ranged from 0.5 gram to 102 grams a day, the average being 24 grams in 24 hours.

Two tablespoonfuls (6.4 grams) about one-half hour after meals and before bedtime, or 2 capsules (0.5 gram) every hour, with 6 to 8 at bedtime were typical dosage schedules.

Increasing the dose, per se, did not give continued and complete comfort in 3 individuals: one with coronary artery disease; another with pulmonary tuberculosis, positive sputum and thorocoplasty, but no demonstrable gastro-

intestinal tuberculosis; and one with hydronephrosis, all of whom had active duodenal ulcers responding to treatment, but who probably also had referred pain from their other diseased systems.

Group III. Eleven of the 23 individuals who had pain related to diseases other than peptic ulcer were relieved of pain, at least temporarily, by resin administered much as in Group II. The relief was not of long duration, however, and the lesions present required individual treatment.

Group IV. Of 56 individuals who had ingested varying amounts of the resin, undesirable effects were of a minor and immediate nature rather than profound and delayed.

Approximately 25 per cent or 16 patients "blamed" the resin for "gagging" because of taste or smell or both (in 7); nausea (in 4); diarrhea, "sour stomach" fullness, or dry stools in individual instances, and esophageal or anal burning,

TABLE 2
The Effects of Resin Ingestion

Patients with peptic ulcer.....	30
Relieved of pain.....	29
Unrelieved.....	1
Patients with pain due to lesions other than peptic ulcer.....	23
Relieved of pain.....	11
Unrelieved.....	12
Total number of patients ingesting resin.....	56
No toxic manifestations.....	40
Undesirable effects.....	16

vomiting, constipation or gas in 2 persons, respectively. More than one type of complaint was reported by some individuals.

Anal burning (and slight bleeding) was reported by an ulcer patient who had taken over 6 grams of resin every hour without any food, and who developed diarrhea. Esophageal burning was especially prominent in the patient who had both an esophageal and duodenal ulcer. He had congenital shortening of the esophagus.

If a patient had not been constipated before being placed on resin therapy, he did not develop constipation. Those whose complaint had been constipation of long duration were not improved by the resin.

No obvious delayed detrimental effects were noted in 12 patients who had taken an average of 1 to 2 grams a day (1 to 2 capsules after meals and before bedtime) for 12 or more months. One patient has taken 32 grams daily and another 7 grams without weight loss, changes in the routine blood count, urine, and gross stool examination, or sedimentation rate. No permanent gastric anacidity has been noted. No clinical avitaminosis was observed, and physical examinations have been unrevealing of abnormalities ascribable to the resin.

COMMENTS

Group I. The method employed was crude and the findings in this group are inconclusive except in the case in which 6.4 grams of the resin was administered half-hourly. Gastric free acidity under these conditions can be kept very low. However, patients may not like to take this dose so repeatedly, and any resultant nausea or vomiting will interfere with its administration in a given patient. The presence of food or other substances in the stomach, the length of time the resin remains in the stomach, the contact time and size of the particle, the rate of acid secretion as well as any periodic variation in pH, might modify the practical needs of such large doses. The ideal size of the dose and its relationship to pain control remain unsolved.

Group II. That ulcer pain can be relieved by this resin seems to have been demonstrated. However, the relationship between pain and the amount, time of administration and physical state of an anion exchange resin remains obscure.

Patients and observers, knowing that a "new" remedy was being employed, may have misinterpreted the actual conditions. Time will reveal the true nature of any results at first reported too favorably.

That the resin cannot be considered a cure-all, nor a complete preventative was shown by the facts (1), that recurrences and complications did occur, even while the resin was still being taken by mouth, and (2), that symptom relief and ulcer healing were neither synchronous nor synonymous.

Since most of the patients observed were cooperative and actively at work, it was hoped that an anion exchange resin would be a convenient adjunct to ambulatory treatment. This resin may well be of value in individualized cases, but its use routinely as an antacid and ulcer cure to the exclusion of other treatments is not suggested.

Group III. That pain associated with other gastro-intestinal lesions could be relieved, at least in part, points to a non-specific effect of the resin. However, the mechanism of pain production might be similar in both the ulcer and non-ulcer groups.

Conversely, if definite pain relief does not accompany the adequate use of an anion exchange resin as an antacid in the presence of a peptic ulcer, a complication or some disease elsewhere might be suspected.

Group IV. Since no evidence of serious toxicity was manifested in these patients, any amount of the resin which the patient will take may apparently be administered with impunity over an indefinite period of time. The taste factor did not exclude most patients from its use, and flavoring can perhaps be added or encapsulation employed. If food is eaten regularly, diarrhea and burning might be avoided. If the average dose is 3 grams or less, and not repeated oftener than every 2 hours, vomiting, nausea, and fullness might not

be produced. Since constipation is apparently not produced by the resin, anti-constipation measures need not be considered except in individuals already so afflicted.

SUMMARY

The effect on peptic ulcer pain of an anion exchange resin has been studied in a group of 30 patients, all but one experiencing pain relief. Relief of pain was not synonymous with healing of the ulcer but in some cases healing did occur. In a few cases the ulcer situation became worse while the patient was under treatment.

No serious toxic effects from the use of the resin were noted. Minor side effects sometimes interfered with its use.

Pain relief was observed in cases in which no ulcer was demonstrated.

Preliminary study of acid changes within the stomach of certain patients in the presence of the resin were not conclusive.

An insoluble, non-absorbable anion exchange resin, having properties of speedy action and great acid neutralizing powers, which inhibits pepsin activity; which causes no acid rebound, no constipation and no removal of phosphate or chloride ions from the body fluids, and which has but a slightly unpleasant taste (capable of being overcome) should be of value to patients with peptic ulceration and is worthy of further clinical trial.

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A POLYAMINE FORMALDEHYDE RESIN

III. CHRONIC TOXICITY EXPERIMENT IN RATS

HARRY L. SEGAL, M.D., HAROLD C. HODGE, Ph.D., JAMES S. WATSON, JR., M.D.,
AND HILDA COATES, M.A.

*From the Departments of Medicine, Biochemistry and Pharmacology, The University of Rochester
School of Medicine and Dentistry*

INTRODUCTION

In a recent paper (1) it was shown that a polyamine formaldehyde resin (Amberlite IR-4¹) was effective in neutralizing the acidity of HCl solutions and of gastric juice in vitro. In rats preliminary feeding tests of 28 days duration revealed a low order of toxicity for this resin. These results justified further work to indicate whether this resin or similar resins might be safely and efficaciously used over a long period of time clinically, especially in the treatment of peptic ulcer.

Martin and Wilkinson (2) have confirmed both the acid neutralizing ability of this resin as well as to its non-toxicity in *rats* fed a more extended period (nine weeks). In addition, studies in *dogs* over a period of 3 months and in five *men* receiving 12 grams daily over a period of two weeks revealed no toxic effects. These investigators also found that the acid neutralizing effect was enhanced by decreasing the particle size of the resin.

The present paper describes an oral toxicity study of this resin fed to rats over a period of almost eight months.

METHODS AND RESULTS

The plan of this chronic toxicity experiment was comparable to that used in authors' original article upon preliminary feeding tests of 28 days duration. Diets containing 0, 0.5, 2, and 20 per cent of the purified resin in a Purina Fox Chow mixture were used. Female and male albino rats in groups of ten were placed at weaning on each of the above diets.

The growth curves are shown in figure 1. All of the rats grew well, were in good coat and appeared sleek. Normal feces were found throughout the test; there were no signs of diarrhea. Some slight depressing effect on growth by the diet containing 20% resin was apparent in the males; the females showed no such differences.

At the end of the eight months period, hematological examinations were made using tail blood. Hemoglobin percentage, grams of hemoglobin per 100 ml. of blood, and red blood cell and white blood cell counts were determined

¹ The resin used in this study was supplied by The Resinous Products and Chemical Company, Philadelphia, Pa.

on four rats from each of the feeding groups. No consistent variation was found in any group; all the values appeared to be normal. The hemoglobin percentages ranged from 92 to 119; 12.7 to 16.6 grams of hemoglobin per 100 ml. of blood were observed; red blood counts averaged from 6.9 to 9.8 millions and white blood counts from 7,200 to 18,400. Differential counts were also

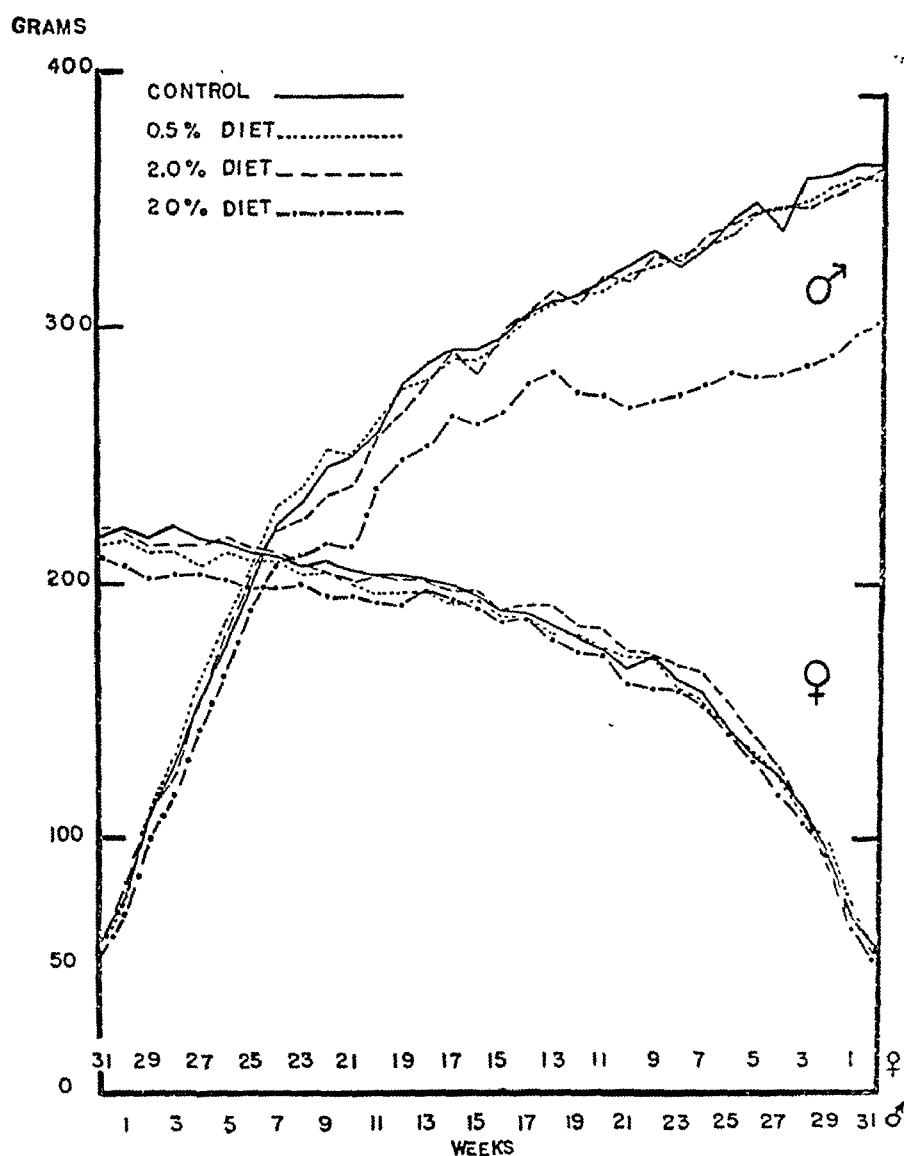


FIG. 1. GROWTH CURVE—RATS CHRONIC RESIN DIET

within normal limits for percentages of polymorphonuclear leucocytes, lymphocytes, monocytes, eosinophils, and basophils.

A few fasting blood sugar determinations were done on control rats (85, 105 mg.%) and on rats fed 20% resin (91, 155 mg.%). Blood chloride values were also obtained on a control rat (587 mg.%; 100 m.eq.) and on 3 rats fed

20% resin (604 to 639 mg.%; 103 to 109 m.eq.). All these values were normal.

After these examinations, the rats were sacrificed with illuminating gas as the lethal agent. Gross autopsies were performed. A number of organs were dissected out and weighed. In each experimental group the average weights of brain, heart, lung, liver, spleen, stomach and kidneys did not differ significantly from the averages for control rats.

Histological examinations were performed by Dr. Roger Terry of the Department of Pathology on the following tissues of each rat: spleen, lung, heart, liver, stomach, small and large intestine, kidney, and brain.

There was no evidence of a toxic reaction in any of the experimental rat tissues compared with the controls with the following possible exceptions. In the *stomach* of 2 rats on the 20% diet there were small areas of squamous epithelium surrounded by glandular mucosa. A third rat also showed what appeared to be a small diverticulum lined by squamous epithelium in the submucosa of the stomach. It may be possible that these structures were the result of mechanical trauma from the resin diet. It is also possible that they were artefacts due to folding of the tissue when the sections were taken. Two control rats showed changes in the sections of stomach tissue; in one was what appeared to be a glandular embryological rest, in the other there was some squamous pearl-like formation and hyperkeratosis at an area of transition between squamous and glandular mucosa. Most of the *lung* sections both of control and of experimental rats showed some pathology. Several showed hyperplasia of the peribronchial epithelium, acute bronchitis, and a few presented early bronchopneumonia. Many showed partial atelectasis and mild congestion. There was considerable iron pigment in the *spleens* of both control and experimental animals which may have represented evidence of infection with Bartonella.

SUMMARY

Synthetic resin in the purified form was studied for its chronic toxicity in rats. Groups of rats were fed diets containing 0, 0.5, 2, and 20 per cent of this resin for a period of eight months. From weight curves, urinary and blood studies and autopsy observations, it was evident that 0.5 and 2% diets of the purified resin exhibited a very low order of toxicity. The rats receiving the 20% resin diet were essentially normal, with the exception of three rats in whom changes were found in the mucosa and submucosa of the stomach.

The over-all toxicity for rats of the resin, Amberlite IR-4, appears to be negligible.

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THE TREATMENT OF PEPTIC ULCER WITH ANION EXCHANGE RESINS¹

A PRELIMINARY REPORT

MANFRED KRAEMER, M.D. AND DAVID J. LEHMAN JR., M.D.

From the Presbyterian Hospital, Newark, N. J.

The use of synthetic resins as exchange adsorbents was first described by Adams and Holmes (1) in 1935. In 1938 one of us, while working with magnesium trisilicate (2) in the treatment of peptic ulcer, discussed acid adsorption as contrasted with neutralization with Mr. Howard Tiger, then Vice President in charge of research, of the Permutit Corporation. Unfortunately, magnesium trisilicate acted ninety per cent by weight as a neutralizer and only ten per cent as an adsorbent. Mr. Tiger had been studying exchange resins in relation to water purification and suggested the use of synthetic resins, because of their ability to remove acids from solution. These substances appeared biologically inert in contrast to the effects produced on the bowel or acid base balance of the blood by all metallic salts. However, he computed that at least one pound of the resin, then available, would have to be ingested daily in order to maintain an intragastric pH of sufficient height to inactivate pepsin and permit healing of an ulcer.

In 1945, Segal (3) and his associates used a Polyamine-formaldehyde resin, (Amberlite IR-4) as an anion-exchange resin on the gastric secretions of rats. They found vigorous stirring necessary to effect prompt adsorption of acid by resin. Feeding experiments revealed the substance to be innocuous. The inactivation of pepsin by the resin was an indirect one, dependent on acid removal by the resin. Again, the large amount of resin required to remove clinical amounts of acid from solution and the need for constant stirring rendered its use impractical in treating peptic ulcer.

In 1946 Martin and Wilkinson (4) reporting from the Research Laboratories, of the National Drug Company, Philadelphia, showed that Amberlite IR-4 was an effective acid neutralizer in amounts practical for clinical use if a fine mesh resin was used. The finer the mesh, the smaller was the particle and the greater was the surface exposed for adsorption of acid.

These papers plus a recent conversation with Mr. Tiger prompted us to begin treating cases of peptic ulcer with resin. We have repeated the acid removal studies of Martin. We have treated eighteen cases of X-ray proven

¹ The resin used in this study was supplied through courtesy of Dr. Steven Horoschak of The National Drug Company, Philadelphia, and is not on the market, and is still limited to investigational use.

peptic ulcer to date. It has been our practice to give a level teaspoonful (about 3.5 gms.) four to eight times a day, as the case required. There have been no toxic effects on the blood or urine, and no sensitivity reactions. The resin did not cause constipation or diarrhea in any of our cases. Two patients complained that the resin irritated the throat. This disappeared on changing to another "lot" of resin. The resin has no taste but has a definite odor (formalin-like). It is insoluble in water giving a "sandy" taste to the mixture of resin and water. The sandy taste and odor can be easily overcome by prescribing the resin in capsule form or by other pharmaceutical means.

CASE REPORTS

Case I. M. G., a forty-eight year old housewife, has had an X-ray proven duodenal ulcer since 1939. Diet, antacids, and antispasmodics had been intermittently effective over the years. Cholecystectomy for stones was performed in 1944 and the ulcer identified. In December 1945 she began to have severe, spasmodic right mid-abdominal pains, associated with heartburn, belching and nausea. Attacks lasted one to two weeks, and were partially relieved by milk, diet, atropine and Amphogel. When first seen by us in June 1946, she was in the throes of a severe exacerbation. She had lost twenty-six pounds in the preceding six months. Gastric analysis showed fasting free acid of ninety-one degrees; blood and urine were normal. Gastro-intestinal X-ray series showed definite duodenal ulcer, with large gastric residue after six hours. She was hospitalized on June 27, 1946 and placed on a strict ulcer diet, given atropine sulphate grains one-two-hundredth every four hours, and one teaspoon of resin every three to four hours. Nightly gastric drainage was performed for the first week. She became completely pain free on July fifth and has remained pain-free to the present time. She has gained ten pounds and is feeling better than she has in years. She remains on an ambulant ulcer diet and continues to take resin.

Case II. E. M., a twenty-seven year old white, single male, was first seen in September 1946. He had had a duodenal ulcer since February 1943, proven by X-ray in an Army Hospital, following an episode of bleeding. He was treated with transfusions and Amphogel and recovered in three months. He remained well until September 1945, when he first noticed post-prandial epigastric pain, relieved by food and milk, and controlled by diet, Atropine and Gelucil. In July 1946, pains recurred and became constant for the first time. Pain then became nocturnal, and was not controlled by milk and cream diet and antacids.

Free fasting gastric acidity was thirty-three degrees rising to ninety-three degrees after a stimulating meal. Gastro-intestinal X-rays showed a duodenal ulcer. He was treated ambulant with Atropine Sulphate, diet and one teaspoonful of resin every three to four hours. He obtained relief in three days; he has remained well to the present time on diet and resins.

Our other sixteen cases had similar histories. By manipulation of diet and resin and antispasmodics we have been able to keep them as symptom free

as the average case under good medical management with salts of aluminum, calcium or magnesium. However in none of these patients were there any symptoms referable to the colon.

SUMMARY AND CONCLUSIONS

From our studies over the past four months, it seems probable that synthetic resins will find a place in the treatment of peptic ulcer. They are innocuous, yet highly effective acid removers. To date, they have shown no ill-effects upon the gastro-intestinal tract. They are valuable substances for controlling gastric hyperacidity without the annoying side-effects of constipation and diarrhea. They cannot upset the acid-base balance of the blood.

In the past six years the synthetic resin industry has grown tremendously because resins have been found more effective removers of acid and alkali than metallic salts. They have been used in such a variety of procedures as to remove the taste of rind from canned fruit juice to the removal of salt from sea water. We predict they will find an important place in the treatment of peptic ulcer.

ADDENDUM: As of December 30, 1946 thirty six cases of ulcer have been under treatment with satisfactory progress.

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REPORT OF A PRELIMINARY CLINICAL TRIAL OF DIBUTOLINE, A NEW ANTISPASMODIC DRUG

GEORGE M. CUMMINS, M.D., GILBERT H. MARQUARDT, M.D. AND M. I. GROSSMAN, Ph.D., M.D.

*From The Wesley Memorial Hospital and The Department of Physiology, University of Illinois
College of Medicine, Chicago, Illinois*

INTRODUCTION

It is our purpose to report in this communication a limited clinical trial of a new synthetic antispasmodic drug, Dibutoline, (dibutylurethane of dimethyl-ethyl-b-hydroxyethyl ammonium sulfate) (Merck) which shows promise of being very useful in the treatment of a wide variety of common diseases that are characterized by smooth muscle spasm. Dibutoline has been shown to possess a direct inhibitory action on the smooth muscle of the intestine as well as an anti-acetylcholine or atropine-like effect (1). The drug has been useful in ophthalmological practice and its possible value in gastrointestinal disorders has been suggested (1).

Dibutoline has been used as an adjuvant or the sole therapeutic agent in the treatment of the following diseases: chronic, non-specific ulcerative colitis, 3 cases; dysmenorrhea, 3 cases; colonic spasm, 4 cases; duodenitis with associated spasm, 1 case; functional pylorospasm, 1 case; and duodenal ulcer with pylorospasm, 1 case.

CHRONIC, NON-SPECIFIC, ULCERATIVE COLITIS

Dibutoline was employed in these 3 cases as the antispasmodic adjuvant in the place of atropine. Each received either 5 or 10 mg. intramuscularly every 3-4 hours day and night for as long as 42 days. All complained of severe abdominal cramping pain and tenderness as well as severe diarrhea prior to treatment. Tincture of belladonna given to tolerance for periods of from 1 to 6 months previously had failed to give symptomatic relief. After the first 2 or 3 injections of Dibutoline, marked alleviation of symptoms was noted—the cramping abdominal pain disappeared completely, the abdominal tenderness became minimal and the stools became less watery and less frequent. In 2 of the cases atropine gr 1/50 or gr 1/300 given subcutaneously every 3 or 4 hours was substituted for Dibutoline for a period of 3 days during which time the recurrence of abdominal pain, abdominal tenderness and an increase in the frequency of the stools was noted. Alleviation of the symptoms was again accomplished by substituting Dibutoline for atropine.

DYSMENORRHEA

In two of these cases the patient had severe pre-menstrual cramping pain for 12 to 24 hours which was not relieved by salicylates and codeine sulfate taken

orally. One patient received 7.5 mg. Dibutoline subcutaneously and obtained complete relief in about 4 minutes, which lasted 12 hours; a second similar dose at the end of this time resulted in no further pain. The other case of premenstrual pain responded in about 7 minutes with complete alleviation of the pain. The third patient who was flowing at the time of injection did not obtain relief after 10 mg. of Dibutoline.

COLONIC SPASM

The first of these cases had had severe recurrent attacks of generalized abdominal pain over a period of 3 years. During the acute attacks atropine sulfate gr 1/75 per hypo had not alleviated the pain. Dibutoline, 5 mg. caused complete cessation of pain for 48 hours, the effect being noted after about 5 minutes. A second similar dose was necessary after 2 days; no pain was experienced for the following 7 days. No other treatment was employed. The second case had had severe abdominal cramping pain for 2 weeks prior to injection of 10 mg. of Dibutoline; complete alleviation of pain occurred after 7 minutes with no recurrence. The third patient had complained of acute episodes of abdominal cramps for a period of 2 years. 10 mg. of Dibutoline was given per hypo with marked relief of pain in 10 minutes; two subsequent similar doses were required during the following 48 hours. The fourth case complained of recurrent attacks of cramping abdominal pain accompanied by diarrhea for a period of 2 years. 5 mg. of Dibutoline was given 4 times daily with alleviation of pain and passage of normal stools after 24 hours.

DUODENITIS WITH ASSOCIATED SPASM

This patient was operated upon for removal of a duodenal diverticulum at which time a severe duodenitis was also noted. Severe right upper quadrant abdominal pain radiating to the interscapular region and the shoulders was controlled by giving 10 mgm. of Dibutoline every 2 to 3 hours on the second post-operative day. Upon discontinuing the Dibutoline on the third post-operative day, the patient was less comfortable after receiving 100 mg. of Demerol 3 times plus atropine sulfate gr 1/150 once.

FUNCTIONAL PYLOROSPASM

In a patient with roentgenologically demonstrable pylorospasm without organic lesion complete relief of pain was afforded in 10 minutes after injection of 10 mg. of Dibutoline. Similar control of pain was noted upon recurrence 8 hours later with another 10 mg. injection.

DUODENAL ULCER WITH PYLOROSPASM

Severe epigastric cramping pain was alleviated in 5 minutes after injection of 10 mg. of Dibutoline. No recurrence was noted in 24 hours.

It is noted in these few cases of smooth muscle spasm in which Dibutoline was used that the drug has proved very effective in alleviating the pain accompanying such spasm. Particularly, useful results have been obtained in ulcerative colitis, spastic colitis, pylorospasm, and premenstrual cramps. Toxic symptoms have been few and minimal when they did occur. Dryness of the mouth was the only side reaction noted. No patient complained of tachycardia, flushing or change in visual accommodation.

We believe that Dibutoline deserves extensive clinical trial as an antispasmodic agent.

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THE EFFECT OF CIGARETTE SMOKING ON MALNUTRITION AND DIGESTION

ALFRED E. KOEHLER, M.D., Ph.D., ELSIE HILL, B.S., AND NORMAN MARSH, M.D.

*From the Santa Barbara Cottage Hospital and the Sansum Clinic Research Foundation,
Santa Barbara, California*

INTRODUCTION

It is a common clinical impression that excessive tobacco smoking is a factor in failure to gain weight in malnutrition and that the cessation of smoking frequently results in improved nutrition. Excessive smoking is also frequently believed to be a factor in the cause or aggravation of certain forms of functional indigestion. Because of the great increase, both in the use of cigarettes and in the incidence of functional indigestion, interest in a possible relationship merits consideration. Accurate scientific data on this matter, however, is scanty and controversial.

Most of the studies on the effect of tobacco on the alimentary tract have been directed toward the effect on gastric secretion and acid formation, particularly with reference to ulcer patients. The results, unfortunately, are conflicting. Bernay and Faure (1) reported that tobacco as well as denicotinized tobacco stimulated gastric secretion and acidity. Similar results were found by Rosenblum (2). On the other hand, Schnedorf and Ivy (3) found no significant change in gastric acidity or secretion after cigarette smoking in sixty human subjects including a group of ulcer patients. In dogs the injection of 0.2 to 1 mg. nicotine had either no effect or caused a depression in acid secretion. These authors did demonstrate that smoking increased salivary flow but that nicotine itself caused no such stimulation. Schnedorf and Ivy also confirmed the previous findings that smoking tends to increase the motor activity of the colon. The observations in the literature give no or little information as to the reason for the common clinical impression that smoking may frequently be a limiting factor in weight-gain in the undernourished. That this impression has a basis in fact is shown in table 1. A group of chronic cigarette smokers who were underweight and had reached a level of maximum weight under a program designed to stimulate weight-gain were advised to stop smoking. Six subjects were selected merely to illustrate that excess cigarette smoking may be a limiting factor in underweight.

DUODENAL SECRETIONS

From the viewpoint of adequate digestion and consequently weight-gain, the concentration of the digestive enzymes is, of course, of primary importance.

To our knowledge there is no evidence relative as to whether or not smoking has any deleterious effect on the amount of enzymatic digestive activity in the duodenum. We have attempted to answer the question of the effect of cigarette smoking on the rate of flow of the digestive secretions, the bile concentration and amylolytic, proteolytic and lipolytic activity of the duodenal secretions as determined by trans-duodenal drainage.

The drainages were obtained by a duodenal tube in the early forenoon without food after the previous evening meal. For the enzymatic activity the digestions were done at 37.5 degrees Centigrade in a special type of incubator in which a shaking platform kept the mixtures in constant gentle agitation. The digestions were all carried out in a phosphate buffered solution at pH 7.0 which is the approximate reaction of the duodenal contents. The results were expressed in the following manner as previously published by the senior author: *Rate of secretion*. Expressed as cc. collected per minute. *Icteric index (bile pigments)*. Dilution of drainage necessary to match

TABLE 1
The effect of stopping cigarette smoking on weight-gain

SMOKING PERIOD				NO SMOKING		
Subject	Sex	No. cigarettes per day	Average wt.	Weeks observation	Gain per wk.	Final weight
			pounds		pounds	pounds
1) J. C.	♂	18 to 25	140 ± 3	8	1.6	152.8
2) R. K.	♂	25 to 30	160 ± 2	10	1.1	171.0
3) M. E.	♀	15 to 25	98 ± 1	12	1.3	113.6
4) E. S.	♀	20 to 25	92 ± 3	8	0.9	99.2
5) A. R.	♂	15 to 20	103 ± 2	10	1.2	115.0
6) I. P.	♀	20 to 30	108 ± 4	36	0.5	126

colorimetrically 0.01 N potassium dichromate solution. *Amylase*. Mg. sugar as maltose liberated from 1 cc. of 1 per cent starch solution by 1.0 cc. secretion in 10 minutes at 37.5° C. *Lipase*. Cc. of 0.1 N NaOH required to neutralize the fatty acids formed from 2 cc. olive oil by 10 cc. secretion shaken (emulsified) in an incubator for three hours at 37.5° C. *Protease*. Mg. of amino-acid + NH₃ nitrogen obtained from 250 mg. casein by 10 cc. secretion shaken in incubator for three hours at 37.5° C.

At the start of the drainage the duodenal secretions were permitted to flow until an approximately constant rate was obtained and the specimen for analysis was then collected for the next hour or until 45 cc. was obtained. The subject then smoked three cigarettes of conventional brands and the second specimen was similarly collected, timed from the beginning of smoking without removing the duodenal tube. By this procedure greater accuracy is obtained than if the smoking experiment was done on a different day, inasmuch as the same conditions are preserved and the tube is in the same position as in the

control period. Furthermore, we have observed that the drainage may vary appreciably from day to day.

TABLE 2
Effect of smoking on the duodenal secretions

Subject	BEFORE SMOKING					DURING SMOKING				
	Icterus	Amylase	Lipase O.I.N.	Pro- tease amino acids	Rate of flow	Icterus	Amylase maltose	Lipase O.I.N.	Pro- tease amino acids	Rate of flow
Non-Smokers										
				mg.	cc./min.		mg.		mg.	cc./min.
1. S. C.	25	1.64	24.0	5.5	0.58	30	2.00	24.5		0.45
2. H. H.	35	2.56	24.0	4.9	3.66	20	2.24	22.7	4.9	2.66
3. E. V.	25	1.04	23.5	4.0	5.70	15	2.34	24.3	4.2	5.00
4. M. B.	70	1.48	27.0	5.1	0.68	30	1.56	24.0	3.6	2.16
5. D. B.	25	1.32	21.0	2.6	2.20	20	0.40	16.4	1.4	1.50
6. W. G.	55	0.96	19.8	6.3	1.16	25	0.68	0.0		0.67
7. C. H.	20	1.24	16.0	2.4	1.57	20	1.56	19.8	3.9	1.00
8. G. P.	30	1.36	3.5	5.1	2.00	40	1.32	19.5	4.3	2.00
9. M. S.	20	3.96	28.0	6.6	1.40	15	4.60	27.5	7.3	0.84
10. G. W.	50	4.62	11.5	7.0	0.73	60	4.68	20.5	6.4	1.75
11. H. L.	10	3.20	26.0	7.6	0.58	15	3.20	24.5	8.7	0.46
Average.....	33	2.13	20.4	5.3	1.84	28	2.23	20.3	4.9	1.68
Difference.....						-5	+0.10	-00.1	-0.4	-0.16
Per cent.....										
Variation from control.....						-15	+4.6	-0.5	-7.3	-8.7
Smokers										
1. R. P.	20	2.64	28.0	5.1	1.75	20	2.36	17.0	4.7	1.20
2. F. T.	5	0.68	18.5	2.3	1.75	0	0.00	18.0	3.2	1.00
3. C. S.	53	1.28	19.0	4.6	0.50	55	1.08	21.0		1.67
4. H. R.	20	3.84	20.5	5.6	0.78	5	5.60	20.5	4.9	3.00
5. E. T.	43	1.32	20.5	3.8	0.63	40	1.32	25.9	4.2	1.50
6. R. B.	25	7.00	26.3	4.7	2.25	1	6.80	16.2	3.4	2.60
Average.....	28	2.79	22.1	4.4	1.28	20	2.86	19.8	4.1	1.83
Difference.....						-8	+0.07	+2.3	-0.3	+0.55
Per cent.....										
Variation from control.....						-28	+2.5	-10.4	-6.8	+4.3

RESULTS

The effects of smoking on the duodenal secretions are shown in table 2. In the group of non-smokers smoking three cigarettes in succession had no significant effect on the secretion of amylase, lipase, or protease or upon the rate of

flow of the duodenal secretions. This was true in spite of the fact that this amount of smoking was distasteful under these conditions to the majority of the subjects. In six of the eleven subjects the bile secretion was diminished during smoking and the average indicated a probable percentage decrease as compared with the control period.

In the group of smokers, all of whom smoked more than fifteen and averaged about twenty-five cigarettes a day, the effect on amylase, lipase and protease was again without demonstrable significance for the number of subjects studied. On the other hand, bile secretion was again diminished similar to, but even to a greater extent than in the non-smoking group. The rate of flow of the duodenal secretions was increased in four of the six cases and the average percentage for the group was definitely increased over the control period.

It is of interest to note that the average values for bile pigments, amylase, protease and the rate of flow for the control period is about the same for the non-smoking and the habitual smoking group.

DISCUSSION

Although excessive cigarette smoking may be a dominant factor in the prevention of weight-gain in under-weight subjects on an adequate dietary program, the adverse effect is not due to a diminution of the secretions of the pancreatic ferments. Schnedorf and Ivy had noted similar results in anesthetized dogs that neither inhalation of cigarette smoke nor the intravenous injection of two mg. of nicotine over a fifteen minute period produced a change in the volume of the pancreatic secretion. These authors found that only if the nicotine was injected intravenously rapidly with a resulting drop in blood pressure was there a retardation of pancreatic secretion.

The excessive smokers who were underweight all manifested a certain indifference to foods frequently bordering on a mild anorexia. Frequently this group mentioned that they had a bad taste in the mouth which ceased after stopping smoking. Cessation of smoking definitely improved the appetite in this group and it is believed that improved appetite and increased food intake was the main cause of weight-gain. Our work in man and also that of Schnedorf and Ivy in dogs lends no support to the view that excessive smoking impairs the secretion of digestive juices to a point where the digestion of food would be impaired.

SUMMARY

Excessive smoking may interfere with proper nutrition in malnourished subjects on a rest and dietary program designed to gain weight.

The smoking of three cigarettes in succession did not significantly influence

the rate of flow or the concentration of amylolytic, proteolytic, and lipolytic enzymes of the duodenal secretions as obtained by transduodenal drainage.

The response to smoking in the non-smoking and smoking group were about the same.

The basal values during the control period before smoking for bile secretion and the digestive ferments was about the same for the non-smokers and smokers.

It is concluded that the gain in weight after cessation of smoking in habitual heavy smokers is due to the increased interest in food and improved appetite and the probable increased caloric intake.

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Section on
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INTERESTING X-RAY FINDINGS IN A CASE OF ACUTE
FULMINATING ULCERATIVE COLITIS

EMIL JOBB, M.D. AND ARTHUR FINKELSTEIN, M.D.

*From the Gastro-Intestinal Service of Dr. H. L. Bockus, The Graduate Hospital of
the University of Pennsylvania*

INTRODUCTION

The usual triad on which a diagnosis of ulcerative colitis is based is a history of bloody diarrhea, characteristic sigmoidoscopic mucosal findings and the roentgen appearance. These x-ray changes are most characteristic in the advanced stages of chronic ulcerative colitis when distortions of the mucosal pattern, loss of haustral markings and a decrease in size of the colon are the outstanding features. However, even these signs at times must be interpreted cautiously. It is more difficult to interpret the roentgen findings in the acute fulminating type of ulcerative colitis, even though the clinical and sigmoidoscopic criteria are present. Indeed, it is considered wise to postpone x-ray studies of the gastro-intestinal tract in the fulminating phase of acute ulcerative colitis until the acute process has subsided somewhat, unless complications arise rendering x-ray study imperative for the intelligent management of the patient.

The following case report presents an interesting clinical picture of partial bowel obstruction associated with signs of peritoneal irritation indicative of impending perforation, and the dramatic roentgen demonstration of large ulcerations of the entire colon. Certainly in the absence of the characteristic sigmoidoscopic findings other causes for the clinical picture would have been seriously considered. The selection of the proper therapeutic procedure, whether medical or surgical, frequently taxes the ingenuity of the best clinician in acute fulminating ulcerative colitis. Surgery of the colon during this acute inflammatory phase involves a notoriously high mortality. In the present

case because of the fear of impending complete obstruction which might have necessitated laparotomy, a barium enema was cautiously given to obtain additional information. This roentgen study demonstrated the absence of any obstructive lesion and thus justified the continuation of conservative therapy despite the marked colonic distention. The visualization of unusually extensive ulcers provided an adequate explanation for the severity of the clinical findings. This case illustrates how extensive the disease process in the colon may be in acute ulcerative colitis and still be followed by complete healing within a relatively short time.

CASE REPORT

On November 1, 1945, a twenty-year old single Jewish male student was admitted to the Graduate Hospital complaining of lower abdominal cramps, left lumbar pains, abdominal bloating and frequent sanguinous, purulent bowel movements of twelve days duration.

The family history and personal history were irrelevant. The past medical history disclosed attacks of measles, chickenpox, mumps and pertussis in childhood. Between the ages of four and five years the patient had repeated episodes of otitis media which required frequent myringotomies.

The present illness began suddenly on October 19, 1945, with isolated episodes of severe peri-umbilical cramps lasting perhaps three to five minutes. For the next few days the patient became conscious of a great deal of borborygmus in addition to the abdominal cramps. On October 21, 1945, instead of having the usual two formed bowel movements, he had four loose watery stools expelled with force and associated with rectal pain. On October 22, he passed a brick-red stool with explosive violence. He was seen by his family physician on October 24, 1945, placed on a bland diet and given antispasmodic, mildly sedative medication. From October 21 to October 27, he averaged four to five loose watery bowel movements daily. The patient developed severe left lower lumbar backache in addition to his abdominal pains which had now become localized in the lower abdomen, particularly in the left lower abdominal quadrant. For two or three days prior to admission on Nov. 1, 1945, his condition had been getting progressively worse. The temperature varied from 99.5° to 101°F. The abdominal pain and backache was constant. Medication, including narcotics, failed to give relief. There had been from eight to ten bowel movements each day.

Physical examination on admission revealed a well developed and well nourished youth, writhing about with severe abdominal pain and appearing acutely ill. His temperature was 99.2° F., pulse was 100, respirations 22 and blood pressure 120/80. The tongue and mucous membranes were dry. Both ear drums were scarred. Examination of the heart and lungs revealed nothing remarkable. The outstanding feature of the abdominal examination was slight abdominal distention associated with diffuse tenderness most exquisite in the left lower abdominal quadrant where one could see and feel a distended loop of bowel. Peristalsis was heard only occasionally.

Blood count: erythrocytes 4,630,000 per cu. mm., leukocytes 4,700 per cu. mm., neutrophils 71 per cent, lymphocytes 29 per cent, hemoglobin 13.5 gm. The urine showed only a slight trace of albumin. The sedimentation rate was 43 mm. at the end of one hour (Westergren). The sigmoidoscope was inserted five inches with the patient in the left lateral position. Two ounces of feculent mucoid somewhat sanguinous material drained out from the bowel. The membrane was visualized with difficulty because of the feces. Those areas seen showed marked edema and engorgement with numerous superficial pinhead sized ulcers with a purulent film over the mucosa. The picture suggested an acute ulcerative colitis or acute dysentery.



FIG. 1. SCOUT FILMS OF ABDOMEN MADE IN THE AFTERNOON OF NOV. 2, 1945

A. In recumbent position, a moderate amount of gas is noted throughout the colon, from cecum to sigmoid. B. In the erect position, multiple fluid-air levels are noted in the colon and probably also in the small intestines. This suggested partial obstruction of the distal colon and possibly also the distal small intestine. Adynamic ileus of small intestine associated with perforating lesion of left colon was also considered.

During the first two and one-half weeks of the patient's illness he averaged twelve to fourteen semi-liquid bowel movements containing a great deal of pus and blood daily. The temperature hovered around 101°F. The pulse ranged from 90 to 100 per minute. Respirations varied from 24 to 26 per minute. On November 2, 1945, the patient became more despondent and continued to complain bitterly of pain, predominantly in the left lower quadrant and in the left loin. This pain was relieved little, if any, by analgesics and sedatives. Distention became progressively more marked. A plain flat film of the abdomen on the afternoon of November 2nd revealed gaseous distention of the colon from the cecum to the region of the mid-descending colon (fig. 1). There were a number of fluid levels in the central part of the abdomen. These were interpreted as distended loops of lower ileum. At this time abdominal examination revealed an almost complete absence of peristaltic sounds

and exquisite tenderness and slight muscle guarding in the lower left abdominal quadrant. Signs of serosal inflammation were unmistakably present and partial obstruction of the lower left colon was considered likely. Usually, marked distention is not seen in association with ulcerative colitis in the absence of serosal inflammation or obstruction. Certainly in the absence of sigmoidoscopic evidence of ulcerative colitis exploration would have been seriously considered.

Fearing the development of complete obstruction which might require laparotomy it was decided to try the very slow introduction of barium into the rectum in order to get additional information. This x-ray study on the evening of November 2nd (fig. 2) showed tremendous gaseous dilatation of the entire colon involving most prominently the ascending and transverse segments. There was an inconstant constriction of the mid-descending colon due to repeated regional spasms, as well as a slight narrowing of the upper sigmoid colon. Myriads of ulcer flecks were seen in the left colon (figs. 2C and 2D) and moderate mucosal coarsening was noted in the hepatic flexure and transverse colon. We believe that the dark halo surrounding the ulcer fleck represents the edematous margin of the ulcer. No previous description of such an appearance in the colon has been found on reviewing the literature, although this halo has been frequently described in reference to peptic ulcers.

On November 5, flat films of the abdomen showed much barium remaining throughout the distended colon; multiple peculiar barium flecks were noted in the right colon as well as the left, being particularly conspicuous in the enormously dilated ceco-colic area (fig. 3). The latter flecks are considered due to ulcers since barium-filled ulcer craters are identified in profile in the descending colon.

On Nov. 7, the patient began to pass more rectal flatus, pain decreased slightly, and the number of stools began to decrease. It was decided to continue conservative management. Fever persisted in spite of the use of both sulfadiazine and penicillin. From November 2 to November 7, in addition to receiving supplements of saline and glucose parenterally, the patient received 3500 cc of plasma and 500 cc of blood. For the next four to five days, he received an additional 1000 cc. of plasma and 1000 cc of blood. The sigmoidoscopic examination on November 15 revealed a deep red-brown mucous membrane, with moderate amounts of mucosanguinous purulent exudate. There were occasional small pinpoint ulcers with some tendency to pitting, and in one or two areas a suggestion of early hyperplastic changes.

During the latter three and one-half weeks of the illness, the patient's condition improved rapidly. His temperature became normal after the first week of his illness and remained so. The distention, pain and tenderness gradually decreased during the fourth and fifth weeks of the illness. By the fifth week the patient was having one to two loose bowel movements per day associated with slight cramps but no blood or pus. The back pain had gradually subsided. A barium enema study on November 27, showed marked pseudopolypoid mucosal changes involving the entire colon, but no definite ulcer craters (fig. 4). Sigmoidoscopic examination on December 2, 1945, revealed a rectal mucosa which was practically normal. There was no edema; no ulcers were seen. In the rectosigmoidal area there were several areas of

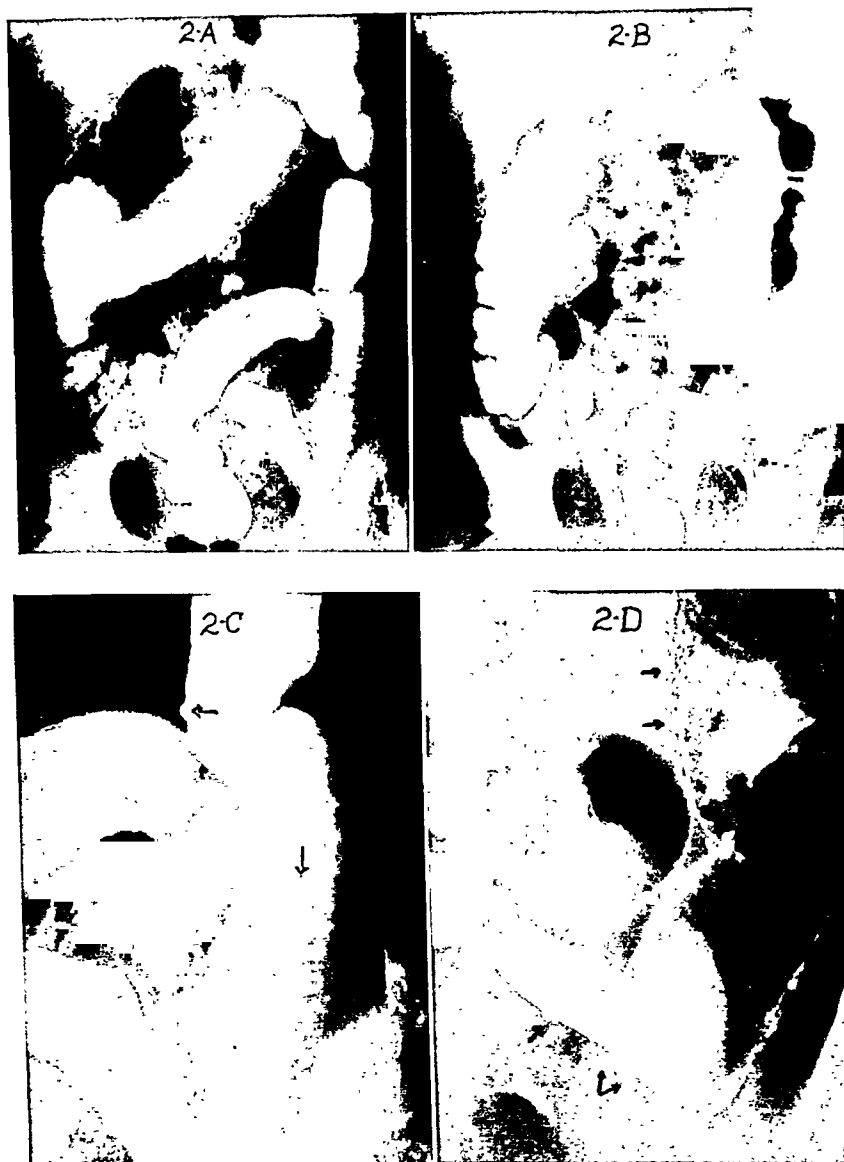


FIG. 2. BARIUM ENEMA IN THE EVENING OF NOV. 2, 1945

A. Disproves any colonic obstruction but demonstrates multiple large ulcers of left colon, and coarsened mucosal pattern of hepatic flexure. B. Reveals constriction in mid-descending colon due to regional spasm. C. "Close-up" of sigmo-colic area showing multiple large ulcer craters in profile and en face (note dark halo produced by edematous margin of ulcer craters; vertical arrow points to a good example). D. "Close-up" of sigmo-colic area after evacuation shows extensive undermining of ulcer craters; best example indicated by double arrow.

congested, granular, hyperplastic mucosa interpreted as areas of healing ulcers. Barium meal study on December 12, 1945, revealed coarsening of the mucosal pattern of the jejunum and slight to moderate dilatation of the distal ileal loops. These

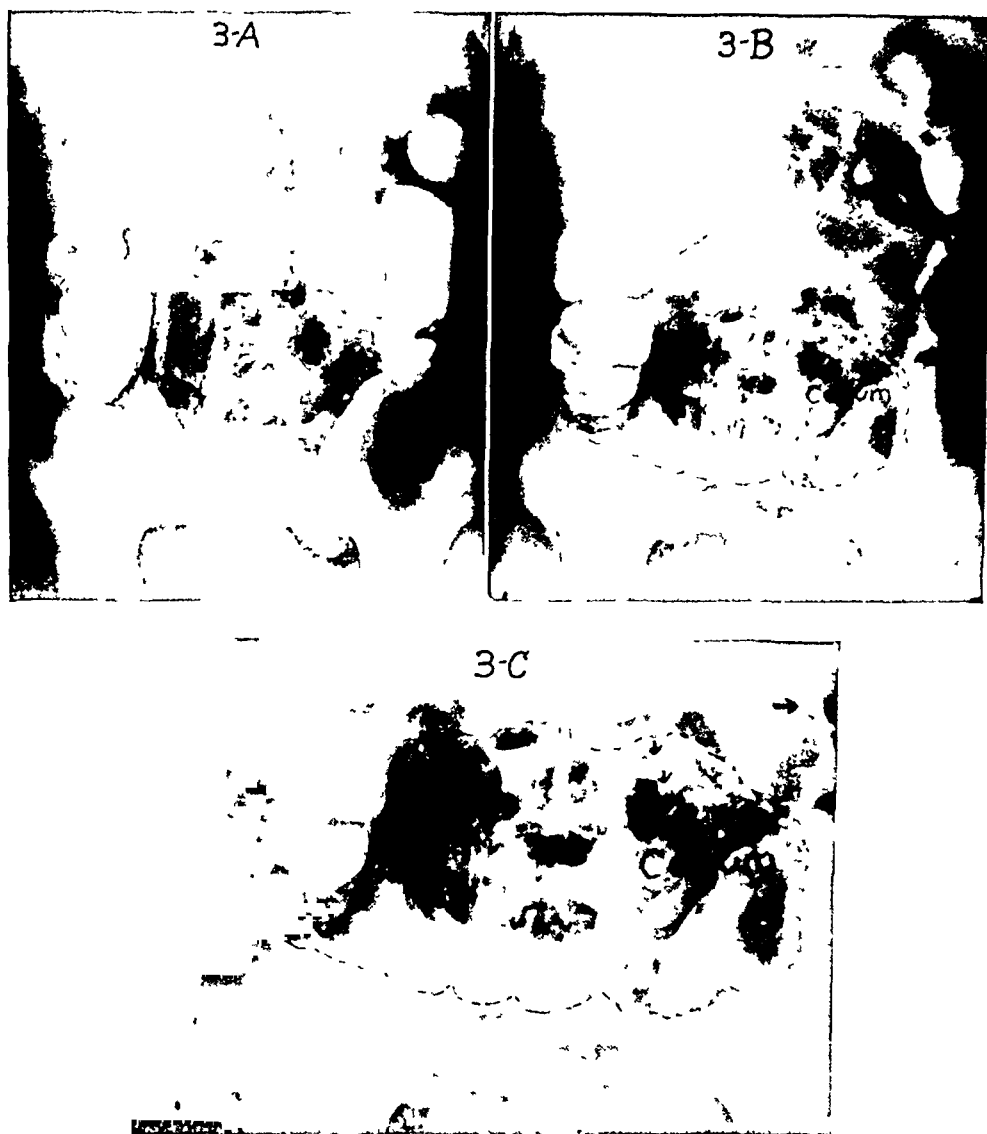


FIG 3. FLAT FILMS OF ABDOMEN ON NOV. 5, 1945

Show: A. Moderate amount of residual barium, and considerable gaseous distention especially in the redundant ceco-colic area. Multiple small oval flecks of barium in ceco-colic region and transverse colon are evidently in ulcer craters, since definite ulcer craters are still visible in profile in the descending colon. B. A few small flecks are indicated by small arrows in ceco-colic area. Note regional spasm in mid-descending colon. C. "Close-up" of ceco-colic area outlined by pencil dots. Small oval flecks of barium in ulcer craters

changes were thought to be due to a minor nutritional deficiency state, as well as the effect of previous peritoneal irritation.

Laboratory examinations during the hospital stay, including frequent fecal

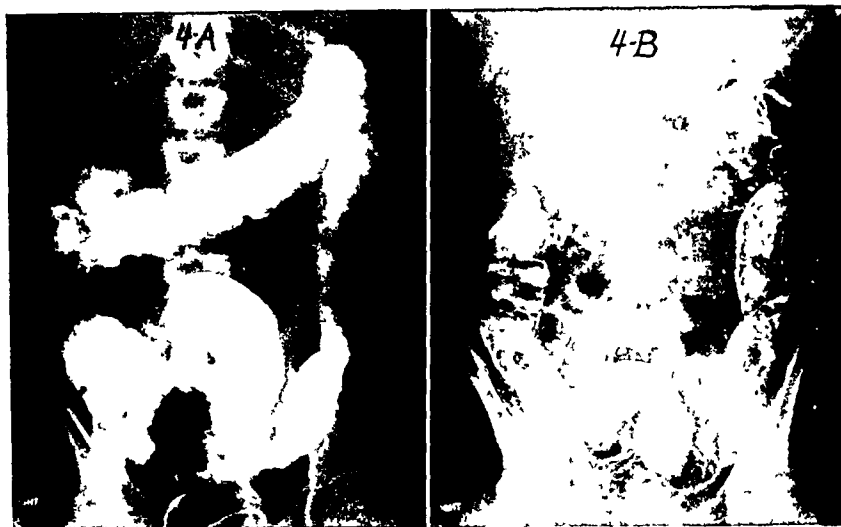


FIG. 4. Barium enema on Nov. 27, 1945 discloses extensive pseudopolypoid mucosal changes seen best in left colon after evacuation (B), but no ulcer craters.



FIG. 5. A Barium enema on March 19, 1946 reveals a fairly normal colonic configuration. In the exposure made after evacuation (B) the mucosal pattern of the descending colon is not well visualized but no ulcers or pseudopolypoid changes are detected

analyses, stool cultures and the various agglutination tests were negative. Blood cultures were negative. The erythrocyte counts throughout the hospital stay remained well over 4,000,000 cells per cu. mm. The leukocytes count varied from

6,500 to 10,400 cells per cu. mm. The differential count remained normal with the exception of one occasion, shortly after admission, at which time the neutrophil percentage was 91. There was a moderate shift to the left. The plasma proteins were slightly below normal. The sedimentation rate on December 11, 1945 was 17 mm. in one hour.

Patient was discharged from the hospital December 13, 1945 in good condition. When last examined on April 8, 1946, he had gained considerable weight and was symptom free. He was having two firm, large, sausage-shaped stools daily. The sigmoidoscope, passed a full distance of 10 inches, revealed no mucosal disease. Roentgen examination of the colon on March 19, 1946 (fig. 5) revealed very little if any evidence of colitis. The colon appeared slightly shorter and perhaps narrower than on the previous examination. Haustrations were absent in the descending and sigmoid colon. There was no evidence of a polypoid mucosal change in spite of the extensive ulcerations previously visualized during the acute process. Our last communication from the patient on July 17, 1946 stated that he remains symptom free and continues to gain weight.

SUMMARY

A case of acute diffuse fulminating ulcerative colitis with x-ray demonstrations of widespread large ulcerations of the colon is reported. The clinical picture was unusual because of symptoms of partial bowel obstruction and peritoneal irritation. Both x-ray and sigmoidoscopic studies demonstrated dramatically the course of healing, within five months, of this rather uncommon type of acute idiopathic ulcerative colitis.

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SPRUE AS A SEQUEL TO THE WAR'S MIGRATION OF MILITARY PERSONNEL¹

STANLEY W. OLSON, M.D. AND JOHN A. LAYNE, M.D.

The military operations of the Allied forces in World War II brought a large number of men and women into tropical areas, and the recognition and treatment of diseases incident to this mass migration constituted one of the major problems of their Medical Departments. The sequelae of these diseases will constitute a problem, not only for the Medical Department of the Armed Forces and the Veteran's Administration, but also for the civilian physician. One of the diseases which may be expected to occur in increasing numbers in the succeeding decade is sprue. Since sprue is an insidious disease, which may produce irreversible changes in the small intestine, the importance of early diagnosis and prompt and adequate treatment is apparent.

We have observed three patients who had returned from the Southwest Pacific Theatre of Operations, and whose symptoms and findings represent, we believe, three stages of this disease, ranging from the advanced and therefore easily diagnosed stage, to the early or incipient stage, where only minimal findings are present. In all three patients the diagnosis of sprue had not been considered until their hospitalization in this country.

CASE REPORTS

Case No. 1. History: The patient was a 33 year old Major, who had had almost constant diarrhea from April 1945, at which time he was stationed in the Philippine Islands, until his hospitalization in this country, in November 1945. At that time the diarrhea consisted of the passage of five to six, or more, bulky, foul smelling stools each day. The stools were light in color and floated on water. He had lost about 45 pounds in weight since the onset of the diarrhea. When hospitalized in this country his chief symptoms were, in addition to his diarrhea, easy fatigability, shortness of breath on mild exertion, and abdominal distress, with the passage of considerable flatus.

Physical examination revealed moderate pallor of the skin, and a rather marked glossitis. The abdomen was mildly protuberant. The remainder of the examination, including proctoscopic examination, was normal.

Laboratory examinations: The results of the examinations of the blood in this patient before and after treatment have been summarized in table 1. Repeated examinations of the feces were negative for the presence of ova and parasites, for occult blood, and for pathogenic bacteria. Barium enema examination of the colon was normal. Free hydrochloric acid was present in the gastric secretion in normal

¹ Presented before the forty-seventh annual meeting of the American Gastroenterological Association in Atlantic City on May 24-25, 1946.

amounts. Examination of the peripheral blood smear revealed macrocytosis, anisocytosis and poikilocytosis. The oral dextrose tolerance test, following therapy, was normal. Radiologic examination of the small intestine performed before treatment showed coarsening and irregularity of the mucosal pattern throughout the jejunum. There was marked segmentation of the barium in the lower jejunum and ileum, with dilatation of some loops of the ileum and jejunum to a caliber of about 50 per cent above normal, and in these loops there was loss of the mucosal pattern. These changes are illustrated in figure 1, which represents the appearance of the small intestine one hour after ingestion of the barium sulfate meal. Following treatment, the jejunal mucosal pattern was more regular; there was no segmentation and only very minimal flocculation. Figure 2 illustrates the practically normal radiographic pattern of the small intestine which was present following therapy. Table 2 illustrates the decrease in the amount of fat in the feces of this patient before and after treatment.

TABLE 1

This table represents the changes which had occurred in the blood of the first patient two months after starting his therapy

	BEFORE TREATMENT	TWO MONTHS AFTER STARTING TREATMENT
Hemoglobin.....	12.8 grams (85%)	16 grams (106%)
Erythrocytes.....	2,830,000	4,980,000
Hematocrit.....	43	50
MCV.....	152	100
MCH.....	45	32
MCHC.....	29%	32%
Reticulocytes.....	2.3%	0.1%
Blood Calcium.....	9.7 mgm.	10.2 mgm.

Progress in hospital: The patient was treated with a high protein, high carbohydrate, low fat diet, with large doses of liver extract intramuscularly (5 units per c.c.), and additional oral supplements of all vitamins. He made a marked objective, as well as symptomatic improvement on this regime, his diarrhea ceased, and he regained his former weight.

Comment: This case represents chronic tropical sprue which was well developed when the patient was first hospitalized in this country. Reversal of the hematologic changes, improvement in carbohydrate absorption and improvement or reversal of the abnormal radiographic pattern of the small intestine occurred following adequate treatment.

Case No. 2. History: This was a 36 year old Medical Officer who developed intermittent diarrhea about 6 months after his arrival in New Guinea in November 1943. The diarrhea recurred intermittently until about April 1945, at which time he was in the Philippine Islands, and it remained constant thereafter until his hospitalization in this country in October 1945. While overseas, cysts of *Endameba histolytica* were found in his feces on one occasion. However, following an adequate

course of anti-amebic therapy, pathogenic ameba were never again demonstrated. His diarrhea, weight loss and increasing fatigue persisted even after his return to this country in July 1945. Glossitis and stomatitis had been present intermittently



FIG. 1. THIS RADIOGRAPH ILLUSTRATES THE CHANGES CHARACTERISTIC OF SPRUE WHICH WERE PRESENT IN THE SMALL INTESTINE OF THE FIRST PATIENT BEFORE THE INSTITUTION OF THERAPY



FIG. 2. THIS RADIOGRAPH ILLUSTRATES THE MARKED IMPROVEMENT IN THE SMALL INTESTINE PATTERN OF THE FIRST PATIENT WHICH HAD OCCURRED TWO MONTHS AFTER STARTING TREATMENT

on several occasions after the onset of the diarrhea. When hospitalized in this country, he was having four loose, bulky stools a day. These were light in color, foul-smelling, and floated on water.

Physical examination revealed him to be 20 pounds underweight and to appear

chronically ill. His skin was dry, dehydrated, and without normal tone. There was redness of the tongue and atrophy of the papillae at its edges. The abdomen was slightly protuberant but there were no palpable masses. The remainder of the physical examination, including prostoscopic examination, was essentially normal.

Laboratory examinations: Repeated examinations of the feces failed to demonstrate endameba histolytica or other ova, parasites or pathogenic bacteria. Gastric analysis revealed normal amounts of free hydrochloric acid to be present. There was no anemia, or macrocytosis of the erythrocytes. A flat type of oral dextrose tolerance curve was present. Other blood chemistry studies, including tests of liver function, were all normal. Radiographic examination of the upper gastro-intestinal tract and small intestine revealed a hyper-irritability of the stomach and duodenum. There was thickening of the mucosal folds of the jejunum and segmentation and flocculation of the barium in the jejunum. Barium enema examination of the colon was normal.

Progress in hospital: The patient was treated in the same manner as that described for the first patient, and on this regime he made marked improvement. His diarrhea ceased, and during the next three months he gained 25 pounds in weight. He was not

TABLE 2
These determinations were performed using a 48 hour collection of feces, and are expressed in percentage of dry matter of feces

	BEFORE TREATMENT	TWO MONTHS AFTER STARTING TREATMENT
Total fat.	52%	21%
Fatty acids.....	40%	11%
Neutral fats.....	12%	10%

able to tolerate more than small amounts of fat in his diet, even at the end of this period, however, without the development of abdominal distress and increased flatulence.

Comment: The diagnosis of sprue was made in this patient because of the history of chronic diarrhea, the appearance of the stool, the flat type of oral dextrose tolerance curve, the presence of glossitis and stomatitis, and the radiographic appearance of the small intestine. Oral dextrose tolerance tests performed after the institution of treatment were normal, as were subsequent radiographic examinations of the small intestine.

Case No. 3. History: The patient was a 26 year old Air Corps pilot who developed intermittent periods of diarrhea beginning when he was stationed in Guadalcanal in December 1942. The diarrhea persisted intermittently after his return to this country in May 1943 until October 1945, when he was hospitalized because of it. He had lost about 25 pounds in weight from December 1942 to May 1943. His diarrhea, during the several months preceding admission, had consisted of approximately three soft, bulky stools a day, and which floated on water. He had some cramping abdominal distress after meals, but had experienced no soreness of the

tongue or mouth. He had received additional supplements of vitamins orally and in fairly large dosage, but these had not improved the diarrhea, although they may have prevented the development of the glossitis and stomatitis.

Physical examination was essentially normal. Proctoscopic examination was normal.

Laboratory examinations: Repeated examinations of the feces for ova and parasites, including endameba histolytica, and cultures of the feces for pathogenic bacteria were negative. Free hydrochloric acid was present in the gastric contents in normal amounts. The hemoglobin, blood counts and blood chemistry were all normal. There was no macrocytosis of the erythrocytes. Oral dextrose tolerance tests revealed a flat type of curve. Radiographic examination of the small intestine was normal except for slight hypomotility. Barium enema examination of the colon was normal, as was the remainder of the laboratory examinations.

Progress in hospital: Because of the nature of his diarrhea, his history of having been in the tropics, and the flat type of oral dextrose tolerance curve, the patient was treated in the same manner as described for the first patient. Following institution of this therapy, marked subjective and objective improvement occurred. His diarrhea ceased, his easy fatigability and other symptoms disappeared, he regained his weight and has remained entirely asymptomatic thereafter.

Comment: We do not believe that a diagnosis of sprue should be made in this last patient. On the other hand, we have no way of knowing whether he would have developed the more typical and more advanced findings of sprue had his condition been permitted to continue. His improvement following institution of a therapeutic regime similar to that used for the other two patients was indeed striking. We believe, therefore, that this third patient represents an example of the clinical syndrome described by Lepore and Golden (1) and which may well represent the early or incipient, and therefore more easily reversible, stage of sprue.

DISCUSSION

Sprue is a chronic deficiency state with a marked tendency to remissions and exacerbations. Its exact etiology is unknown but it is generally believed to be the result of a nutritional deficiency. The essential similarity of the chronic forms of tropical and non-tropical sprue has been demonstrated, and the remarkably beneficial action of liver extract in the treatment of both types of the disease, supports this conclusion. The symptoms of this disorder depend to a large extent upon the alteration of the physiologic processes normally performed by the small intestine. There are other conditions in which the body is deprived of the normal absorptive functions of the small intestine, such as jejuno-colic fistula, extensive resection of the small bowel, and sarcomatous infiltration of the mesentery, which may produce a clinical syndrome similar to sprue.

The functions of the small bowel are those of transportation, digestion and absorption of food. There appears to be no disturbance of digestion of food

in sprue, but the other two mechanisms are grossly altered. Proper absorption from the small intestines depends upon the adequate distribution of the food substances to all the mucosal cells. Normally, this is accomplished by a rhythmic to and fro motion of the food by peristalsis, with a gradual forward progress through the intestine. In addition, the villi have a shortening and elongating action by which they dip into the stream of food as it passes by. When this mechanism is altered, the efficiency of absorption is impaired. Radiologic examination of the small intestine demonstrates that in sprue there is edema of the mucosa, distortion of the mucosal folds and alteration of motility. Although these radiologic changes occur characteristically in sprue, minor changes in the pattern of the small intestine should be interpreted with caution, since similar alterations may occur in apparently normal individuals who show no evidence of a deficiency state (2).

Laboratory evidence of the impaired absorption from the small intestine in sprue is shown by the flat type of oral dextrose tolerance curve and by the decreased absorption of glycine (3) and of fats (4). Absorption of vitamins is also interfered with, and clinical evidences of deficiencies of both the water-soluble and fat-soluble vitamins may be present. The hypocalcemic tetany and osteoporosis which develop in the chronic forms of the disease follow upon the inadequate absorption of Vitamin D and the formation of insoluble calcium soaps in the intestine. Anemia of the macrocytic type and scarcely distinguishable from pernicious anemia, is a characteristic feature of the chronic form of sprue. The development of the anemia in most instances is due to failure of absorption of the antipernicious substance from the bowel.

Therapy of the disease is dependent upon the administration of adequate amounts of some substances contained in crude liver extract, in addition to a low fat, high protein and high carbohydrate diet, plus additional supplements of all vitamins. Oral administration of brewer's yeast will produce a remission of the disease if given in large enough doses and before irreversible changes have occurred in the small bowel. As a result of the recent reports (5, 6, 7) of the therapeutic effect of synthetic *Lactobacillus casei* factor ("folic acid") upon sprue, it would appear probable that there will soon be further advances regarding both etiology and therapy of this disease.

In order to prevent the development of chronic and possibly irreversible changes in the mucosa of the small intestine, it is important to institute therapy early. In untreated individuals who have had the disease for many years, permanent changes may have occurred in the small intestine so that improvement is maintained only by continued and intensive parenteral liver therapy. In these individuals it is sometimes not possible to do much more than correct the glossitis and the macrocytic anemia, and eventually they succumb to malnutrition.

Therefore, great care must be exercised in the evaluation of chronic diarrhea occurring in returning servicemen. Physicians who have treated missionaries and trades people returning from the tropics have observed that the symptoms of sprue may appear as long as five to ten years after the individual's return to a temperate climate. The obvious necessity of recognizing amebic and bacillary dysentery in individuals who have had a chronic diarrhea need not be further emphasized. Negative examinations of the feces for pathogenic bacteria and for parasites, and normal radiographic examinations of the large intestine, however, do not necessarily indicate that the individual's disease is a functional one. Nor does the finding of amebae or pathogenic bacteria eliminate the possibility that the patient may have sprue in addition. Many servicemen returning from the tropics have had dysentery. In case No. 2, the patient had had amebic dysentery, and all three patients had been in areas where dysentery was common. It may be expected, therefore, that some of these individuals will have sustained damage to the small intestine, which, by interference with the absorption of essential food substances, may predispose to further dysfunction of the small intestine and the development of the sprue syndrome.

CONCLUSIONS

1. The development of the sprue syndrome in three servicemen who had returned from the Southwest Pacific Theatre of Operations is reported.
2. Sprue may develop in individuals who have previously had diarrhea of bacillary or parasitic origin and which has produced sufficient damage to the intestinal mucosa to impair absorption of essential food substances and thus predispose to further dysfunction of the small intestine.
3. Sprue may produce irreversible changes in the small intestine; therefore early diagnosis and prompt and adequate therapy are imperative.

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EDITORIALS

ACHES AND PAINS AND SORENESSES DUE TO PSYCHOGENIC RHEUMATISM

The gastroenterologist is constantly seeing patients who hope that with the clearing up of their indigestion and the cure of their sore colon, they will lose the aches and pains which they have all over the body. Practically always they are disappointed, and unfortunately the physician commonly fails to make a satisfactory diagnosis because he is not acquainted with psychogenic rheumatism and it does not occur to him that all the aches and pains and sorenesses can be referred to the periphery from a disturbed brain. Perhaps many of the aches partake of the nature of paresthesias. In older persons such symptoms may follow a small unrecognized apoplexy.

In a fine article published in the May, 1946, number of the "Annals of Internal Medicine," Hench and Boland, who during the war were active in the Rheumatism Center of the Army and Navy General Hospital at Hot Springs, Arkansas, stated that "psychogenic rheumatism, the musculoskeletal expression of functional disorders, tension states, or psychoneurosis, is one of the commonest causes of generalized or localized aches and pains in muscles or joints or both." It may exist alone or may occur as a functional overlay of some rheumatic disease, such as fibrositis or rheumatoid arthritis. Hench and Boland felt that better than the term "psychogenic" or "psychosomatic" rheumatism would be "psychoneurosis manifested by musculoskeletal complaints," but doubtless the term "psychogenic or psychosomatic rheumatism" will persist because it is shorter.

During the war many constitutionally inadequate soldiers unconsciously fled into illness and complained of many distresses in the muscles and joints. Examinations failed to show anything except signs of neurosis. Some 20 per cent of the patients admitted to the Rheumatism Center were without signs of real arthritis.

To make the diagnosis the physician must usually differentiate psychogenic rheumatism from primary fibrositis. In general it can be said that fibrositis puts its victims at the mercy of changes in *external* environment, such as bad weather with heat, cold, or humidity; these are the factors that make the patients worse. Rest or exercise also influence them for better or worse. On the other hand psychogenic rheumatism puts its victims at the mercy of changes in *internal* environment. The forces that influence them are variations in pleasure or depression, excitement, mental distraction, worry or feelings of fatigue.

TABLE 1

*Tabular differentiation between fibrositis and "psychogenic rheumatism"; generalities**

	FIBROSITIS, PRIMARY TYPE	"PSYCHOGENIC RHEUMATISM"
General attitude	Coöperative, earnest, "objective"	Tense, anxious, "subjective," defensive, antagonistic
Chief complaint	"Joints hurt and feel stiff"	"Can't quite describe it, doctor. It's like..."
Chief symptoms	Aching, soreness, stiffness, fatigue	Burning, tightness, weakness, numbness, tingling, queer or tired sensations
Time of day when symptoms are worse	Morning and/or late afternoon	Inconstant—often continuous day and night
Aggravation or amelioration dependent on:	External or physical environment	Internal or mental environment
Effect of mental preoccupation: (theatre, movie, bridge, etc.)	No definite relief, symptoms intrude	Often marked relief but perhaps "pays for it afterwards"
Symptom analysis		
1. Pain:		
Amount	+ to ++	+ to +++
Constancy	Varies in intensity during day: worse in morning, better at noon, often worse again later in day	Tendency to be constant, "bad all the time"
Duration	Hours or days	Momentary or constant, "no different," getting worse
Location	Remissions, exacerbations	Often not anatomical
Migration	Anatomical	Bizarre, hemalgia, etc.; may follow no anatomic pattern
2. Stiffness	May not migrate; if so migrates in anatomical fashion	Minimal or not present
3. Fatigue	Worse after much rest (jelling). More marked in early morning. Better after mild exercise.	Jelling not characteristic
	A.M. on waking; 0 to +	Early A.M. + to +++
	P.M. ++	May be constant
	"Disability causes fatigue"	"Fatigue causes disability"
Effect of rest	After prolonged rest—worse (jelling)	Improvement or no effect
Effect of exercise	Better, "limbers up"	Worse during and after
Effect of applied heat	Temporary relief—hours	Variable—often worse
Effect of weather	Worse when cold and damp. "Weather prophet."	Variable

TABLE 1—*Concluded*

	FIBROSITIS PRIMARY TYPE	"PSYCHOGENIC RHEUMATISM"
Effect of therapy: In general Patient's attitude Aspirin	Temporary relief Admits relief Temporary relief—hours	"Nothing helps me, doctor" Defies finding a cure Usually no relief (aspirin futility), or "never tried it" (aspirin inutility)
Physical therapy	Temporary relief	Variable—often worse
Response to examination:	Coöperative; local tenderness consistent	Fearful, resistant; "touch me not" reaction
"Extras" (associated functional complaints)	0 to +	+ to ++++ Bizarre limps and postures, headaches, globus hystericus, sighing respirations, precordial pains, insomnia, nervousness, tremor, etc.

* From Hench, P. S. and Boland, E. W.: The management of chronic arthritis and other rheumatic diseases among soldiers of the United States Army. *Ann. Int. Med.* 24: 808-825 (May) 1946.

The table from Hench and Boland's paper is highly instructive.

Helpful diagnostically to the army physicians was the fact that really rheumatic soldiers were usually docile, quiet and well behaved. They asked little of the medical officer. Those, however, with psychogenic rheumatism behaved more like the usual "neuro" who complains at great length and wants to take up a lot of his physician's time. In private practice one can often suspect the presence of a psychogenic rheumatism when the pains and aches have been constant over the course of years. Fibrositic aches and pains are more likely to come and go. If a psychogenic rheumatism produces pain in the muscles over the region of the liver, the diagnosis of cholecystitis is generally made and a "slowly-emptying gallbladder" is removed. Always then the symptoms go on unchanged, or if they disappear for a while they soon come back.

W. C. A.

COMMENT

PSYCHOSOMATIC GASTROINTESTINAL PROBLEMS IN THE UNITED STATES ARMY

In these days of starvation, rations and rationing it is no small wonder that the gastrointestinal tract has become so voluble in symptomatic expression. As Chief of a Gastrointestinal Section in an Army General Hospital which received large numbers of casualties from the African invasion, and later as Chief of Service at installations receiving casualties from all battle fields, it soon became apparent that the majority of our patients had gastrointestinal symptoms such as diarrhea, hunger pain and abdominal discomfort which could not be explained on the basis of organic disease. There were sufficient findings in previous records to show, for example, that specific dysenteries were present at one time. As our experience increased it became clear that we were dealing primarily with severe psychosomatic disease focused on the gastrointestinal tract, and that the symptoms were the evidences of abnormal conditioned reflexes, autonomic nervous system imbalances and in fact, disturbances of the total personality. Extraordinary observations came to our attention such as one individual who had had fifty-nine gastrointestinal roentgenologic studies in an unsuccessful effort on the part of the organicist to demonstrate structural change.

This brings up the question of therapy as it was practiced in the Army for these patients who had functional disorders. The average doctor simply had no time to explain to them the mechanisms of their illnesses nor often did he understand them himself. At the other extreme, the psychiatrist had no time to individualize or psychoanalyze. Each realized that a number of these soldiers could be helped if properly assigned. The battle of proper assignment for medical purposes was by no means a minor one. The whole problem was summarized in the words of one G. I. Joe who said, "a guy in the Army who has something wrong with him stands a good chance of being goofed off unless some test shows it; if you have something that can be seen, that's O. K., you'll get good care but if the doctors can't see it you're out of luck".

As a general rule, these patients were not dealt with properly in the Army nor for that matter, as far as I am able to observe, are they yet being given the time, patience and understanding they need in civilian life. The day has come when we must realize that the brilliant diagnoses of organic disease or the attempts to treat psychosomatic disturbances of the total personality by a pat on the shoulder and "everything is all right" attitude, are no longer commendable in comparison with a better understanding of the problems of

functional disease which is needed in perhaps 70 per cent of our practice of medicine. Both the doctor and patient must recognize that emotional factors and past experiences contribute to present illnesses. We have gone beyond the period when the patient has either frank organic or frank functional disease. Whatever type of disease he has, be it organic or functional, it is a disease which must be interpreted and evaluated in terms of personality types. The Army erred in doing countless tests of every description when its medical staff and all concerned should have recognized that the majority of the patients were suffering from what, for want of a better term, is called psychoneurosis. Col. Walter B. Martin expressed this view when he said "too many x-rays have been made, too many consultations requested, too many laboratory procedures carried out, and too little thought given by the attending physician to the patient as an individual and to his particular requirements."

Some of us who have spent the last few years in the Army have learned a new language, an organ language, spoken by men in uniform undergoing varying degrees of anxiety and tension. That so large a number of these men should speak through their gastrointestinal tracts should have been expected when one recalls the mishandling of food in the Army, the poor preparation of bulk food, the monotony of the various rations, the changing shifts, and conditions making it difficult to regulate physiologic functions, all these coupled with fear, resentment, frustration, sleeplessness, dust, dirt and darkness, and in many instances, the countless miles from home, loved ones and security, make it easier to understand the gastrointestinal rebellion. This cycle is the actual enactment in terms of disease of the contributions of Cannon, Pavlov and Freud.

In a report from the Mediterranean Theater in which 122 cases of chronic dyspepsia were thoroughly investigated, using, as the authors state, all the laboratory procedures available, the conclusion was reached that psychoneurosis was the most common finding overseas in chronic dyspeptics with vague abdominal distress.

Psychosomatic medicine may not be new but certainly we must change our methods of dealing with the patients. In the Army clear-cut psychoneuroses were often treated brilliantly but many of the organ expressions of nervousness were commonly passed over much too superficially.

Medical care for this group of patients is still in a chaotic condition. This does not mean to say that "the record of the U. S. Army Medical Department during the war should not be justly acclaimed", and I have no desire to obscure in the slightest the fact that in this war the soldiers of this country were better cared for than ever before. "The wounded were saved from death and were returned to military effectiveness in numbers never before considered possible" (DeBakey). But I do want to say that those with psychosomatic

troubles did not fare so well. Seldom did a physician sit down with one of these patients long enough to understand his problems and to make them understandable to him. Few were trained to admit to these G. I.'s that their complaints were real and then to explain to them how such symptoms could arise in the absence of organic disease. In all fairness to the medical officer it should be pointed out that he often labored under the difficult circumstance of seeing large numbers of men in a limited time and had to sift out those who were unfit for soldiering from those who were trying to get out of work and danger and also from those who were genuinely psychosomatically ill.

The experience in the Army has hurled a challenge at the Medical profession, and I now hope that we will accept it and gradually, through better undergraduate and post graduate education and greater effort on the part of all of us, remedy the situation.

SAMUEL MORRISON

BOOK REVIEWS

MODERN ATTITUDES IN PSYCHIATRY. *Iago Galdston, James H. Wall, William C. Menninger, Edward Weiss, G. Canby Robinson, and Franz Alexander.* Columbia University Press, New York, 1946. 154 pp. Price \$2.00.

This is a series of lectures in the March of Medicine series. They were given primarily for laymen at the New York Academy of Medicine. The speakers were Rhoads, Galdston, Wall, Canby Robinson, Alexander, William Menninger and Weiss.

There is much in this little volume to help the physician who is trying to learn something about psychosomatic medicine and the ways of helping persons with neuroses.

EXPERIMENTAL HYPERTENSION. *William Goldring, Richard J. Bing, Eduardo Cruz Coke, W. D. Collings, L. W. Donaldson, M. L. Goldberg, Harry Goldblatt, B. Gomberg, Arthur Grollman, C. A. Johnson, Oliver Kamm, Luis F. Leloir, H. Minatoya, W. G. Moss, Eric Ogden, Irvine H. Page, John W. Remington, L. A. Sapirstein and G. E. Wakerlin.* The New York Academy of Sciences, vol. III, pp. 1-180. 1946.

This little volume will be welcomed by all those physicians who today have been hearing of research being done in the problems of hypertension, but have not been able to follow it closely enough. Here, they will find chapters on different phases of the subject written by men like Page, Goldblatt, Goldring, Grollman and others who have been doing most interesting work in this field.

CONTRIBUICAO AO ESTUDO DE HEREDITARIEDADE NA ETIO-PATOGENIA DA ULCERA DO ESTOMAGO E DO DUODENO. *Joao Galizzi, M.D.* Belo Horizonte. 1946. Pp. 191.

It has always seemed probable that one of the main factors, if not the main one, in the production of peptic ulcer is a hereditary predisposition. Every physician of experience can remember many families in which several members were afflicted with ulcer. Other persons who may have free acidity around 80 units and a typical ulcer temperament will live out their lives without ever getting any ulceration of the stomach or duodenum. Apparently they lack the necessary predisposition to actual ulceration. Dr. Galizzi has investigated a large number of ulcer families and has shown how ulcer crops up again and again in generation after generation. For instance, in his family number 139 four out of six sibs had ulcer. In another family there were six out of ten sibs with ulcer.

In the group of 373 persons with ulcer he found 42% with a history of other cases of ulcer in near relatives. There were 69% of the 373 with relatives with ulcer and with gastrointestinal troubles, some of which might have been due to ulcer. In a control group of 154 patients without ulcer there were only 5% who had near relatives with ulcer.

ANTIBIOTICS PARTS I AND II. Published under editorship of *Roy Waldo Miner*, Annals of the New York Academy of Sciences, vol 48, art. 2. Pages 31-218.

This paper-bound volume of 218 pages is full of useful information which must be of tremendous interest to many physicians today.

On page 143 Doctors Rake and Richardson note that when penicillin was being produced in surface cultures, Type F predominated. Later when deep fermentation came into use G was the predominant type. Following changes in the strain of mold they used and in methods of fermentation and extraction, preparations now usually contain a mixture which is mostly F, K and G. Penicillin X is usually present only in very small amounts, except in penicillin which is produced by surface culture.

There has been a steady improvement in the purity of penicillin. With this of course there has been an increase in the number of units per milligram of material obtained. In spite of all this advance, however, commercial penicillin today must still be considered a highly impure substance. The very best preparations still contain some 25% of material which is chemically and biologically not active penicillin.

Penicillins are strong acids, with a pH around 2.8. Since the free acid is rather unstable, salts are used.

Rake and Richardson discuss the problems of sensitization to penicillin. They say it is not clear yet whether this sensitization is due to the penicillin itself or to the impurities that go with it.

ABSTRACTS OF CURRENT LITERATURE

FRANKLIN HOLLANDER

Associate Editor in Charge of Abstracts
Mount Sinai Hospital, New York City

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MOUTH AND ESOPHAGUS

GASTON, E. A., AND TEDESCHI, C. G. Adenolymphoma of the parotid and submaxillary salivary glands. *Ann. Surg.*, 123: 1075 (June) 1946.

The term adenolymphoma describes a tumor composed of epithelial and lymphoid tissue. The terms papillary cystadenoma lymphomatosum and cystadenoma lymphomatosum are used to describe papillary and nonpapillary variations of the same tumor.

Of several theories on the origin of these tumors, that proposed by Warthin in 1929—to the effect that the lesions arise from a "heterotopia of mucus membrane from the pharyngeal entoderm"—seems the most acceptable one. The authors found that a total of 94 such tumors of the parotid gland have been reported. These occurred predominantly in males, by a ratio of 4.5 to 1.

The tumors grow slowly, causing facial disfigurement rather than pain. They have been tolerated by the patient for periods varying from a few months to over 30 years before they were excised. The lesions typically are well encapsulated, and usually can be removed with minimal danger to

branches of the facial nerve. Three cases of benign adenolymphoma are described by Gaston and Tedeschi. A fourth case showed clinical and morphologic evidence of a malignant tumor, comprised of epithelial cells and lymphoid cells. The authors suggest a classification of adenolymphomatous tumors wherein this exceptional lesion would be designated an adenocarcinoma lymphomatosum.

LEMUEL C. MCGEE.

STOMACH

VENDEL, S. The principle of evacuation of the stomach in infants and pretermatures. *Acta Physiol. Scand.*, 11: 380 (June) 1946.

The time of gastric evacuation varies very considerably in different individuals and even in the same individual on repeated examination. It is difficult to imagine that this should really apply to infants who, in most of their other vital functions, display so marked a regularity. Nearly all previous examinations have been done by means of X-ray studies but only the initial and final points of the evacuation curve of the stom-

ach can be determined exactly enough by this method. To follow the entire course of evacuation another technic was applied, the volume of gastric contents being measured at regular intervals by aspiration through a stomach tube. One hundred ten experiments were carried out on 27 children, aged 1 week to 11 months. From these observations, the author has demonstrated that the stomach in infants empties with extreme regularity, following usually a rectilinear curve; the emptying rate depends upon age and the constituents of the meal, and the variations tend to be much less extensive than previously accepted.

ALBERT CORNELL.

LEWITAN, A., AND NYGAARD, K. K. Roentgen demonstration of a benign intramural tumor (fibromyoma) on the greater curvature of the stomach. *Radiol.*, 46: 590 (June) 1946.

A case of an intramural tumor of the stomach is described. The clinical symptoms were due to a shallow ulcer of the lesser curvature of the stomach. The gastric analysis revealed an absence of free hydrochloric acid in the stomach contents. The roentgenological studies showed a loss of normal serrations on the greater curvature. This area was about 4 cm. long; it appeared constantly, but could be obtained only on minimal right oblique rotation. This area contracted as a whole. The indentations proximal and distal to the involved portions of the stomach were very deep, and an incisura effect was thus produced. In the erect position, a semicircular area opposite the incisura angularis was noted, corresponding in size to the lesion.

FRANZ J. LUST.

BEAVER, M. G., GENDEL, S., AND PAPPER, E. M. Total gastrectomy for complete carcinomatous involvement of the stomach. *Am. J. Surg.*, 71: 813 (June) 1946. This single case report reveals a scirrhous carcinoma of the stomach of the linitis plastica type, successfully treated by total gastrectomy. The necessity for careful preoperative preparation, scrupulous operative technique, and thorough postoperative care is obvious.

The patient was a 41 year-old white soldier, with a preoperative X-ray diagnosis of antral carcinoma of the stomach. The abdomen was opened through a transverse incision, and after total gastrectomy, an esophago-jejunostomy was performed. A Miller-Abbott tube was threaded through the anastomosis for postoperative decompression. The surgical technique and details of anesthesia are fully described and illustrated. Three months after an uneventful surgical convalescence, evidence of abdominal and thoracic metastasis appeared.

MICHAEL W. SHUTKIN.

SCOTT, W. G. Radiographic diagnosis of prolapsed redundant gastric mucosa into the duodenum, with remarks on the clinical significance and treatment. *Radiol.*, 46: 547 (June) 1946.

Prolapses of the gastric mucosa are not rare; in a group of adult males, they occurred as frequently as gastric ulcer. Prolapse of redundant gastric mucosa produces symptoms that may be suggestive, but not characteristic enough to permit of a clinical diagnosis. The condition should be suspected in duodenal ulcer patients with atypical histories, in patients who are refractory to an ulcer regime, and in those who have recurrences when placed on solid foods.

The diagnosis of a prolapse of the gastric mucosa is established largely by Roentgen examination. The filling defects are characteristic and should not be confused with those produced by duodenal ulcers, duodenitis, or other disorders of the duodenum and pylorus. The typical filling defect in prolapse of the gastric mucosa is a negative "cauliflower-like" defect in the base of the duodenal bulb, opposite the pylorus, varying in size and shape during a single examination and on repeated examination. Such defects can be overlooked at fluoroscopy, and this should always be supplemented by "spot films" for the most desirable method of examination. Since large prolapses of the gastric mucosa which produce symptoms are a cause of gastric hemorrhage and may result in a partial pyloric obstruction, the roentgenologist should always be on the lookout for them. He must distinguish them from

other duodenal defects, and report them to the referring physician for evaluation.

The treatment in early and moderate prolapses is medical until such time as repeated and severe attacks or complications occur. In the large prolapses, and in those complicated by repeated hemorrhages or partial pyloric obstruction, surgical measures are indicated. These include excision of the redundant folds of the mucosa and usually a pyloroplasty.

FRANZ J. LUST.

BOWEL

BAKER, H. L., AND HALLEY, H. Neurofibroma of the small intestine with massive hemorrhage. *Ann. Surg.*, 123: 1067 (June) 1946.

Herein are reported 2 instances of neurofibroma of the small intestine with massive hemorrhage. The first patient, a male, 37 years old, had episodes of tarry stools irregularly for 10 months prior to his first admission to the hospital. Because of spasm and deformity in the duodenal cap, shown by roentgenography, the patient was given medical management for peptic ulcer for an additional 7 months. The stools again became tarry and an exploratory celiotomy was performed. The duodenum was found to be normal. About 17 inches from the ileocecal valve a dusky red, hard tumor, 3.5 cm. in greatest diameter, was found in the lumen of the ileum. It was pedunculated, the stalk being attached to the antimesenteric border of the intestine. The surface of the tumor showed evidence of both old and recent bleeding.

The second patient was a female of 33 years who had noted tarry stools irregularly for 3 years. On admission to the hospital she showed mild shock with an erythrocyte count of 2,600,000 and hemoglobin of 56%. The intestinal bleeding persisted and she received 36 transfusions of blood, totaling 20 liters, within a week. On the eighth day the bleeding stopped. No satisfactory cause for the loss of blood was found and the patient was discharged from the hospital. She was re-admitted 9 months later because of further tarry stools, and operated upon. A firm pedunculated tumor, measuring 5 cm. in its greatest diameter, was found in the

ileum attached to the antimesenteric border about 5 feet from the ileocecal valve.

Both tumors were encapsulated and showed no evidence of malignancy. This experience serves to remind the clinician that, while benign tumors of the small intestine are rare, they bleed readily and must be considered in the differential diagnosis of obscure intestinal hemorrhage.

LEMUEL C. MCGEE.

KIRSCHNER, B. Acute fulminating ulcerative colitis—treatment with streptomycin.

N. Y. State J. Med., 46: 525 (Mar.) 1946.

This is the first case on record in which streptomycin was used to treat acute ulcerative colitis in civilian practice. The patient failed to respond to other measures, and was moribund when streptomycin administration was begun. Spectacular improvement followed, but the disease terminated fatally as a result of a pulmonary embolus from a thrombosed leg vein.

PHILIP LEVITSKY.

SHRAPNEL, B. C., JOHNSON, C. M., AND

SANDGROUND, J. H. Oral emetine in the treatment of intestinal amebiasis. *Am.*

J. Trop. Med., 26: 293 (May) 1946.

Twenty patients suffering with amebic dysentery were treated by means of emetine hydrochloride administered enterally in the form of enteric coated tablets. Seven individuals received 1 grain per day for 12 days, 6 others 2 grains daily for 6 days, 3 patients were given somewhat larger doses, and 4 children received comparatively smaller amounts. No severe toxic reactions were observed. Fifteen cases out of the 20 were cured. Four patients were symptom-free, although they continued to show amebae in the stool, and one case failed to respond to treatment.

PHILIP LEVITSKY.

GALAMBOS, A., AND MITTELMANN-GALAMBOS, W. Diverticulosis and diverticulitis of the colon. *Rev. Gastroenterol.*, 13: 171 (May-June) 1946.

The incidence of diverticulosis of the colon, as noted upon X-ray examination with barium enema, ranges between 4 and 10%; in the cadaver, the incidence varies from 0.8 to

7%. It appears to occur equally in both sexes, but is more frequently found in patients over 40 years of age who are obese and of hypersthenic build. In addition to numerous other factors, inherent weakness in the bowel musculature (particularly about the entrance or emergence of vessels), and an inflammatory process have been considered as the etiologic factors. The true cause is unknown, however.

The diagnosis of diverticulosis of the colon is dependent upon X-ray examination, while superimposed diverticulitis is evaluated clinically. It is emphasized that colonic diverticula, with or without inflammatory change, can be associated with other gastrointestinal disease. Because of the silent character of the disease, diverticulitis and diverticulosis may be overlooked.

C. WILMER WIRTS, JR.

DICKSON, J. A., PARKHILL, E. M., AND KIERNAN, P. C. Large retroperitoneal metastasis from a so-called carcinoid of the small intestine. *Surg. Gyn. Obs.*, 82: 675 (June) 1946.

Carcinomas of the small intestine are comparatively rare, comprising about 3% of all intestinal cancers. The so-called carcinoid tumors constitute approximately one-fourth of this group.

A case of carcinoid of the ileum with a large retroperitoneal metastasis is presented, illustrating some of the important surgical and pathological aspects of carcinomas of this type. While the ideal form of surgical management seems to be as radical a removal of the primary lesions and any metastatic foci as is feasible, the strategic location of the small bowel prevented any attempt at excision. Nevertheless, it was possible to remove the primary lesion in the ileum with the involved mesentery, and thus relieve any further possibility of obstruction.

This presentation indicates that these neoplasms can no longer be regarded as benign and harmless, for eventually they will infiltrate and metastasize. However, because of their slow growth, the patient may live for many years in good health. These so-called carcinoids of the small bowel are considered to be grade one (Broder's method) carcinomas of the carcinoid

type, to distinguish them from ordinary adenocarcinomas of the intestinal tract. This designation indicates their slow growth and low malignancy. It was also felt that the histopathologic picture of those neoplasms which had metastasized was similar to the picture of those which had not metastasized, and hence it is impossible to predict on the histopathologic basis which of these neoplasms will metastasize.

FRANCIS D. MURPHY.

FINESTONE, E. O. Injury to the ureter during appendectomy. *N. Y. State J. Med.*, 46: 1239 (June) 1946.

A case of retrocecal gangrenous appendicitis is reported. At operation, a localized abscess was found, in which the right ureter formed part of the wall. When the appendix was removed, a small aperture was seen in the right ureter. This was sutured, and the abscess was drained transperitoneally. The patient made an uneventful recovery.

PHILIP LEVITSKY.

CHESTERMAN, J. T. Neurogenic ileus. *Brit. Med. J.*, 4456: 830 (June) 1946.

Neurogenic ileus is due to a local or general flattening of intestinal gradients. It may be spastic or distensive in type, and the factors producing it may affect the extrinsic nerves or act directly upon the neuromuscular mechanism of the bowel. The symptomatology is in accordance with the factor causing the ileus, the type of ileus, the site of obstruction, the degree of obstruction, and the length of bowel involved. So-called passive ileus is a distensive variety in which venous stasis has become so marked that a vascular intramural obstruction complicates a neurogenic ileus. Mild degrees of traumatic ileus occur after every laparotomy; recovery is spontaneous though occasionally the ileus persists. In a few cases, the distension increases to such an extent that active measures become necessary to alleviate the condition. It is important to realize that neurogenic ileus in these cases may be a local condition—which, if unrelieved, may spread, especially if venous stasis occurs in the affected loops—or it may become a local condition after recovery from the initial post-operative general loss of tone and

movement. Other causes listed by the author include retroperitoneal hemorrhage, injury to the lumbar vertebrae, pneumonia, meningitis, typhoid fever, and intraperitoneal infections.

JOSEPH B. KIRSNER.

LIVER AND GALL-BLADDER

McLAUGHLIN, E. F. Choledochus cyst.

Ann. Surg., 123: 1047 (June) 1946.

A true cyst of the common bile duct presumably involves a congenital malformation. Some degree of obstruction seems to be present regularly where symptoms are produced. Its rarity is shown by the fact that reviewers of the subject as late as 1943 were able to find but 175 reported cases. The condition is said to occur more often in the female than in the male, and more often in children than in adults. A diagnostic triad of (1) abdominal pain, (2) tumor mass, and (3) jaundice forms the typical clinical picture. The surgical treatment has thus far shown a mortality rate of 58%.

McLaughlin describes a case of choledochus cyst. The patient was a colored male, 22 years of age, who complained of a "knot" in the right hypochondrium after eating. He lost 25 pounds in weight prior to his admission to the hospital. Roentgenologic studies repeatedly demonstrated a large ovoid mass in the right upper abdominal quadrant displacing the hepatic flexure caudally. It was further observed that "irregular gas pockets superior to the mass represents an extension from the tumor." Choledochus cyst was considered the most probable diagnosis preoperatively.

At operation, a liter of "chalky-yellow material" and light bile was aspirated from the cyst. The gall bladder, containing gas, and a short common duct were attached separately to the upper surface of the cyst. After the cyst was dissected away, a small portion of the dome into which the above structures opened was anastomosed to the duodenum. The patient lost his jaundice and pain after the surgery.

LEMUEL C. MCGEE.

MOESCHLIN, S. Die Herkunft der Blutplasma-Zellen bei der Hepatitis epidemica anhand von Milzpunktaten (Origin of

plasma cells in the blood in epidemic hepatitis). *Gastroenterologia*, 71: 97 (1946). Early in the course of epidemic hepatitis, typical plasma cells appear in the circulating blood and usually range from 5 to 10% of the total white cell count. Splenic puncture reveals that the spleen contains large numbers of both immature and mature plasma cells. These observations support the view that the plasma cells in the peripheral blood are derived from lymphatic tissue and not from the reticulum cells of the bone marrow, inasmuch as no increase in plasma cells is found in the bone marrow.

CHARLES A. FLOOD.

NICOD, J. L. L'hépatite épidémique. Pathogénie. Anatomie pathologique (Pathogenesis and pathological findings in epidemic hepatitis). *Gastroenterologia*, 71: 62 (1946).

Epidemic hepatitis begins as a hepatitis rather than a hepatosis. Pathologically there are necrosis of the liver and inflammatory changes. Complete healing with restitution to normal may occur, or there may be fibrosis with partial regeneration, or a progressive cirrhosis may develop. The jaundice may be due to mechanical plugging of bile canaliculi, but the author favors the hypothesis that the jaundice is of parenchymal origin and results from leakage between bile ducts and vascular channels after injury of the hepatic cells. The livers of patients dying in hepatic coma characteristically show changes which have been present for a long period, even when the clinical history is of short duration. Autopsies of 3 premature infants, born of mothers who had had epidemic hepatitis during pregnancy, showed no manifestations of hepatitis, which suggests that the virus of this disease does not penetrate the placental barrier.

CHARLES A. FLOOD.

URECH, A. Störungen im Zuckerstoffwechsel nach Hepatitis epidemica. (Disturbances in carbohydrate metabolism following epidemic hepatitis.) *Gastroenterologia*, 71: 83 (1946).

In epidemic hepatitis, it has been shown that the glucose tolerance test is often abnormal, the blood sugar curve being either

abnormally high or prolonged. The author reports 3 patients with hepatitis who were found to have developed diabetes coincidentally. These patients were found to have glycosuria and abnormal glucose tolerance curves, and one patient later developed polydipsia and polyuria requiring insulin to control the diabetes. One patient, a child, had complete recovery with return of glucose tolerance to normal 5 months after onset. The other 2 patients continued to have abnormal glucose tolerance curves many months after onset, one of them also having evidence of persistent liver disease lasting for at least 4 months after onset. These observations are in contrast with the more frequent findings of an abnormally low blood sugar during acute hepatitis. The author suggests that these were cases of true diabetes in which the disease became manifest during an acute hepatitis.

CHARLES A. FLOOD.

WHIPPLE, A. O. Factors common to surgical lesions of the biliary tract. *Bull. N. Y. Acad. Med.*, 22: 281 (June) 1946.

The author calls attention to the three factors that determine the pathogenesis of every lesion of the biliary tract requiring surgical therapy. These factors are as follows: first, disturbed metabolism of cholesterol and salts of the bile acids, resulting in gallstone formation; secondly, infection or inflammation; and third, obstruction. Singly or in combination, one or more of these factors is present in the pathogenesis of every biliary tract lesion requiring surgery. A knowledge of these factors and their location in the different parts of the biliary tree is of the greatest help in the diagnosis of the lesions, in determining the indications for therapy, in following the postoperative course of the patient, in treating the complications, and in giving the prognosis after operation.

ALBERT CORNELL.

BANCROFT, F. W. Treatment of chronic cholecystitis, with and without stone: Indications and contraindications for choledochostomy. *Bull. N. Y. Acad. Med.*, 22: 292 (June) 1946.

The author discusses various types of chronic cholecystitis without stone formation, in-

cluding cholesterosis, chronic catarrhal cholecystitis, and the chronic fibrous variety. The etiology of chronic cholecystitis without stones is still a disputed problem. Extreme caution must be exercised in operating on patients when there is no evidence of biliary calculi. If no help is received from cholecystograms, the Meltzer-Lyon test may be of aid. The B-bile containing bile-stained bacteria or leucocytes is suggestive of chronic cholecystitis. It is the impression of the author that surgeons have too often explored the common duct unnecessarily, with increased morbidity and mortality. He concludes that if the common bile duct, although dilated, does not appear thickened or inflamed, one is relatively safe without incising the duct, unless there are definite indications for it.

Aspiration of the common duct by needle puncture is an aid in determining if there be stones in it. Clear bile without flakes of fibrin is a fairly good indication that no stone is present. However, caution must be used even with a fine needle, as bile is apt to leak from the puncture hole for a considerable time; drainage of Morrison's space must be established in cases where this has been done if the duct is not opened. If the duct is opened immediately, cholangiograms taken on the operative table are a safeguard to assure the complete removal of calculi. With proper equipment, this should not lengthen the operative time to any great degree and may save the patient a secondary operative procedure.

In conclusion, the author stresses the importance of a primary atraumatic cholecystectomy and, insofar as possible, some protection of the common duct in the operative procedure. He has found no method of common duct drainage that seems harmless if a large series is analyzed.

ALBERT CORNELL.

HUTCHINSON, W. R. S. Gas gangrene of the gall-bladder. *Brit. Med. J.*, 4458: 915 (June) 1946.

Gangrenous cholecystitis due to *Cl. Welchii* is seldom encountered. The author reports such an instance in a 56 year-old male who experienced severe pain in the right hypochondrium for 3 days. The abdomen was

slightly distended, with extreme tenderness and rigidity in the right hypochondrium. At operation, the peritoneal cavity contained a considerable quantity of foul-smelling, thin, brown fluid. The gall-bladder was grossly distended, edematous and hemorrhagic, and most of the fundus was obviously gangrenous. Two small stones were palpated in the cystic duct. Cholecystectomy was easily performed and the wound was closed in the usual manner with a drainage tube to the gall-bladder bed. The mucous membrane of the gall-bladder was necrotic, shaggy, and of a dark brown color. Culture of the mucous membrane yielded a pure profuse growth of *Cl. Welchii*. The patient received 20,000 units of polyvalent anti-gas-gangrene serum intramuscularly, and a total of 20 g. of sulfapyridine. He gradually made an uneventful recovery.

The sequence of events is believed to have been as follows: onset of the disease with an attack of gall-stone colic; impaction of the stone, which resulted in congestion and edema of the gall-bladder, together with stasis of its contents; and subsequently, secondary infection by *Cl. Welchii*.

JOSEPH B. KIRSNER.

HICKEN, N. F., AND CORAY, Q. B. Spontaneous gastrointestinal biliary fistulas.

Surg. Gyn. Obs., 82: 723 (June) 1946.

Study of 15 cases showed that one of every 25 patients requiring surgical therapy for disorders of the biliary tract possesses some variety of internal biliary fistula. The best treatment was prevention—by removing gall-stones before they initiate undesirable complications, and by treating peptic ulcers with gastric resection. New growths and surgical trauma were also etiological agents. A preoperative diagnosis of gastrointestinal biliary fistula cannot be made from clinical findings alone. Careful roentgenographic diagnosis affords the only method of making an accurate preoperative diagnosis. The characteristic roentgenographic findings in the various types of internal biliary fistulas are described.

Cholangiograms performed on the operating table afford an excellent method of visualizing the gall bladder, fistulous tract, and entire biliary tree. They determine

location and ramifications of the fistula and clearly depict the size of its orifices. Also, they permit accurate localization and differentiation of existing choledochal obstructions, thus providing the surgeon with an accurate blueprint of the problems confronting him.

The mortality in 13 operative cases was 30%. In 4 patients who died, extensive remedial procedures were carried out at the initial operation which led to the advisability of using multiple operations, particularly a decompression of the common bile duct as the primary procedure.

FRANCIS D. MURPHY.

HEUER, G. J., AND GLENN, F. The surgical treatment of acute cholecystitis. *Bull. N. Y. Acad. Med.*, 22: 283 (June) 1946.

From 1932 to 1945, a total of 527 patients with acute cholecystitis were operated upon. There were 13 deaths, a mortality rate of 2.46%. Cholecystectomy was performed in 460 patients, or 87.4% of those subjected to operation. Cholecystostomy was performed in 67 cases (12.6%). Cholecystostomy was reserved for patients too ill to withstand cholecystectomy or for those in whom cholecystectomy presented excessive difficulties. Nevertheless, cholecystostomy was followed by 5 deaths.

In determining the type of operation to be done, the gross appearance of the presenting pathological changes is of importance. The patients with simple acute cholecystitis are in general best treated by cholecystectomy. In cases of gangrene, perforation, peritonitis, or abscess formation, the procedure varies; the details are fully discussed. Common duct exploration in acute cholecystitis is limited to those patients with unequivocal indication of common duct obstruction, even though it adds an additional risk.

The common duct was explored in 47 of these patients, an incidence of 8.9%. Stones were recovered in 29 of these, or 61.7%. In the entire series of 527 patients, there was a mortality rate of 5.14% in 175 patients who were 50 years of age and over. This indicates the definitely greater risk associated with them. In the group less than 50 years of age, there was a mortality rate of 1.13%. Arteriosclerosis, hypertension, and diabetes

are more common in those with biliary tract disease than in a corresponding number without it. A deleterious effect upon the vascular system may be interrupted by operating in the earlier decades.

Acute cholecystitis represents an early phase of the disease. Given a patient with a definitely established diagnosis of acute cholecystitis, the authors' policy is to provide for surgical treatment as soon as adequate preoperative preparation has been carried out. This differs from the so-called conservative attack, which considers these patients as a medical problem and leaves them in their homes. Under the latter circumstances, complications may develop and result in a greater number of deaths before they are recognized.

ALBERT CORNELL.

ANEMIAS

FROMMEYER, W. B., JR., SPIES, T. D., VILTER, C. F., AND ENGLISH, A. Further observations on the antianemic properties of 5-methyl uracil. *J. Lab. Clin. Med.*, 31: 643 (June) 1946.

Synthetic 5-methyl uracil (thymine) was administered in large daily dosage to 6 patients with pernicious anemia in relapse. All of them showed a satisfactory hematologic response. In one case, the response was duplicated after a period of 45 days during which no therapy was given. It was concluded that synthetic 5-methyl uracil, given orally in daily dosage of 4.5 g. or more, is a potent anti-anemic substance for patients with pernicious anemia in relapse.

EDGAR WAYBURN.

ULCER

MOSCHCOWITZ, E. Essays on biology of disease. Chapter 13—Peptic ulcer. *J. Mt. Sinai Hosp. N. Y.*, 13: 25 (May-June) 1946.

The elucidation of the etiology of peptic ulcer confronts the writer with the difficulty that despite its frequency, the initial phase of this disease is not known. This is due to the fact that the stomach has hitherto been an inaccessible organ. Thus far, the one positive clinical criterion of a peptic ulcer is a Roentgen-ray examination, but this, unfortunately, is diagnostic only after the

ulcer is fully matured. It is possible that the earliest mucosal manifestation may be in the form of an erosion or a circumscribed granulomatous change. Serial gastroscopy offers the hope that this phase of peptic ulcer may be clarified in the future.

In recent years, the view is steadily gaining ground that peptic ulcer is a psychosomatic disease. It appears that peptic ulcer, like all the hyperkinetic diseases, is a disease of civilization. Since the transition can not be observed in the human being, the problem as to how these psychological influences are transmitted into peptic ulcer must be answered through the experimental production of the ulcer. Such experiments prove that the acid factor is vital in producing peptic ulceration. The author gives further proof that the acid factor is a fundamental conditioning factor. In addition, there is every reason to believe that hypersecretion precedes the initiation of human peptic ulcer.

Peptic ulcer may be regarded as a hyperkinetic disease, which means that a large part of the mechanism whereby it is created is the result of a protracted exaggeration of one of the normal bodily functions. This exaggeration is mediated through the autonomic nervous system. The claim that "chronic gastritis" is the cause of peptic ulcer has contributed nothing to the etiology because the "cause" is still obscure. The author outlines his conceptions of the biology of this disease and discusses the healing of peptic ulcer as well as its attendant complications.

ALBERT CORNELL.

NASIO, J. Influence of some vitamins and hormones in the prevention of experimental cinchophen peptic ulcer. *Rev. Gastroenterol.*, 13: 195 (May-June) 1946. Vitamins A, B₁, B₂, C, D₂, and K, as well as nicotinamide and nicotinic acid did not prevent the development of cinchophen ulcers in dogs when administered separately. Vitamin C given simultaneously with the cinchophen appeared to have a protective effect in 60% of the animals; vitamins B₁ and B₂ and calciferol prevented a weight loss as great as that obtained in the controls; vitamin K manifested no effect; and nico-

tinamide appeared to increase the severity of the ulceration and gastritis.

Stilbesterol given with cinchophen parenterally prevented the development of ulcers in 100% of male dogs, and in 22% of female dogs. The stomachs of most of the test animals, particularly the males, presented an apparent hyperplasia of the gastric mucosa.

The production of cinchophen-ulcer in dogs appeared to be prevented by the administration of synapoidin in 65%, of estriol in 60%, and of antuitrin-S in 40% of the animals.

C. WILMER WIRTS, JR.

BOLEN, H. L. Relationship between uremia and peptic ulcer. *Rev. Gastroenterol.*, 13: 229 (May-June) 1946.

The author discusses the relation of pyloric obstruction, nephritis, and uremia. Reference is made to the literature suggesting that the pathologic changes in the duodenum may play an etiologic role in the development of nephritis. Two patients are described in whom nephritis and uremia developed subsequently to duodenal ulcer.

C. WILMER WIRTS, JR.

PROCTOLOGY

RIGDON, R. H., AND FLETCHER, D. E. Multiple argentaffin tumors (carcinoids) of the rectum. *Am. J. Surg.*, 71: 822 (June) 1946.

The rectum is an extremely rare site for carcinoid tumors; since 1942 only one such case has been reported.

A case of multiple carcinoids in the rectum was observed by the authors at autopsy. The patient was a colored male of sixty who died of a dissecting aortic aneurysm soon after admission. Beneath the mucosa of the rectum were innumerable nodules varying in size from only a few to 10 mm.; they were movable, rubbery in consistency, and grayish-white in cut section. The nodules extended from the mucosa to the muscle, and after impregnation with ammoniacal silver, some of the granules were black while others were yellowish-brown in color.

They apparently arise from the argentaffin cells in the crypts of Lieberkühn and are

potentially malignant, though neither ulceration nor metastasis was present in this case. This is the fourteenth case of this type reported to date.

MICHAEL W. SHUTKIN.

ARNHEIM, E. E. Congenital malformations of the rectum and anus. *J. Mt. Sinai Hosp. N. Y.*, 13: 6 (May-June) 1946.

Congenital malformations of the rectum and anus comprise an important group of anomalies in infancies. These anomalies may involve the rectum, the anus, the urogenital organs, or combinations of these structures. The author discusses the embryology, pathogenesis, and classification of these anomalies. The treatment varies with the type of anomaly; it may involve a simple surgical procedure or a complex series of reconstructive operations. The author reports a successfully treated case which illustrates the difficulties in management of a high rectal pouch and recto-vaginal fistula. A preliminary colostomy, followed by staged operations, resulted in a cure of this case of atresia of the rectum.

ALBERT CORNELL.

BACON, H. E. Abdominoperineal proctosigmoidectomy for cancer of rectum. *Am. J. Surg.*, 71: 728 (June) 1946.

This experience of over 5 years includes a series of 461 cases of carcinoma of the anus, rectum, and pelvic colon; and the results obtained with the technique of "proctosigmoidectomy", as designed by Babcock, are reviewed. There were 265 males and 196 females, of which 424 were subjected to operation. The operative mortality for the latter group was 5.8%; for the resected series it was 6.1%. The operability rate was 91.9% and the resectability rate was 80.4%.

Contrary to earlier opinion, the inferior zone of spread for this type of tumor is relatively unimportant; the sphincter musculature may be preserved, provided the lower border of the growth is six cm. or more above the anal margin.

All patients are admitted to the hospital 5 to 7 days prior to operation. During this interval, the fluid, caloric, nitrogen, and electrolyte balances are restored to normal.

The complete preoperative routine also includes sulfonamides, vitamin supplements, blood chemistry, catharsis, irrigations, and use of an indwelling Foley catheter. During the operation, which is performed under fractional spinal anesthesia, 500 cc. of whole blood is administered. Following the operation, which is fully described, the post-operative routine is likewise observed rigorously.

Patients are out of bed on the sixth day, and many leave the hospital on the eleventh or twelfth day. Transplantation of an abdominal colostomy to the perineum, with or without resection, was performed in 84 cases with but one death. Chemotherapy has been a valuable factor in preventing peritonitis, and its administration for 6 days preoperatively is recommended.

MICHAEL W. SHUTKIN.

SURGERY

SUGARBAKER, E. D. Coincident removal of additional structures in resections for carcinoma of the colon and rectum. *Ann. Surg.*, 123: 1036 (June) 1946.

The author reports on 220 patients with colonic or rectal carcinomas, treated in a midwestern hospital which accepts only indigent patients. The average duration of symptoms was 18 months; 67% had lost more than 15 pounds in weight prior to hospital admission. Thirty-one patients were not subjected to surgery. Of the 189 patients who underwent surgical exploration, 147 (78%) had a resection of the lesion. Fifteen patients (10%) in the group of resections received the surgery for palliation alone. The remaining 132 resections were undertaken with hope of cure. Forty-two of these patients had adjacent structures removed in addition to the bowel. These were portions or all of the genital tract, portions of the bladder or ureter, segments of small bowel, femoral nerve, common iliac artery and vein. Eight (19%) of the 42 cases died within 5 weeks following operation. Fifteen others died later of their cancer or are living with recurrent metastatic disease. It is emphasized that the 19 living patients, who showed no further evidence of their disease an average of 2 years after operation, constitute justification for ex-

tensive surgery rather than palliation whenever survival is possible.

LEMUEL C. MCGEE.

LAHEY, F. H. Gastric surgery. *New Eng. J. Med.*, 234: 809 (June) 1946.

This presentation is intended primarily for physicians interested in the general practice of medicine. In a thoroughly concise manner, the author discusses many of the conditions in which surgery is applicable in disease of the stomach, duodenum and jejunum. From a wealth of experience, and with great clarity, the author discusses surgical procedures in the following conditions: hiatus hernia, peptic ulcer of the esophagus, carcinoma of the cardia and lower esophagus, gastric ulcer, gastric carcinoma, leiomyoma of stomach, total gastrectomy, duodenal ulcer, jejunal ulcer, and gastrojejunocolic fistula. A detailed discussion of the technical, surgical procedures is not included.

The mortality rates in the 4 types of peptic ulcer—gastric, duodenal, jejunal and gastro-jejunocolic fistulas—are given, as well as those for radical and palliative operations for malignant lesions of the stomach. The type of lesions in which total gastrectomy has been applied in 39 cases, and the total mortality in this group, are included; also the change between the mortality rate in the first 46 cases and that in the last 43 cases. Some of the measures by which the unsatisfactory end results of surgery for gastric cancer can be improved are stated. The mortality rate following transthoracic resection of the lower end of the esophagus and cardiac end of the stomach is reported again in two groups of cases, in order to demonstrate the improvement that has come with added experience and improved selection. Hiatus hernia, peptic ulcer of the esophagus, and leiomyoma of the stomach are discussed, as are gastric ulcer, duodenal ulcer, jejunal ulcer and gastrojejunocolic fistula, and experiences and mortality rates in handling this group of cases are given.

IRVING GRAY.

STANTON, N. B. A device to simplify end-to-end anastomosis of the large bowel. The elimination of unequal diameters

of the two segments to be anastomosed.

Am. J. Surg., 71: 809 (June) 1946.

To secure an equal diameter of the proximal and distal ends of the left colon after resection for a carcinoma, air is introduced per rectum with a Weber insufflator. Following the application of modern preoperative principles, the air is introduced after the abdomen is open but before the tumor is resected. Anastomotic and rubber-covered clamps control the level of the air, and permit extirpation of the new growth. Since the equalized diameters of the free ends are held by the anastomotic clamps, suture in three layers secures adequate union. There have been no accidents, peritonitis, nor deaths in the author's series of cases.

MICHAEL W. SHUTKIN.

HORSLEY, G. W., AND MICHAUX, R. A. Surgery of colon as seen in an overseas general hospital. Surgery, 19: 845 (June) 1946.

The ideal treatment for injury of the large bowel is exteriorization. If this is not possible, a proximal colostomy should be done. The loop-colostomy is the preferable one in that it can be done easily, shunts the fecal current efficiently, and lends itself to a more satisfactory repair. Regardless of the type of colostomy employed, it should be established through an incision separate from the original one. A glass rod or tube should be used to prevent retraction of the loop. When the colostomy is opened, a longitudinal incision should be employed with $\frac{2}{3}$ of it on the oral side of the supporting rod. Closure should be completed in the transverse axis of the bowel to prevent constriction.

In the series of 111 cases reviewed, only one showed evidence of hepatitis. Apparently, this had been feared unduly, as a sequella to repeated transfusions of blood and plasma which all of these cases had necessarily received. When complicating injuries are present they should be adequately treated before the colostomy is closed. If the colostomy is of the spur type, the spur must first be crushed and then the edema allowed to subside.

Before operation, the distal bowel must

be thoroughly cleaned. A liquid diet should be employed for 24 hours preoperatively. Catgut closure of the stoma is satisfactory, and the sutured bowel is anchored to the under surface of the peritoneum which, with the muscle and fascia, is then closed in separate layers. The skin is left unsutured. Gastric and duodenal suction, with 2000 cc. of 5% glucose in saline and one unit of plasma administered per day, are continued for 3 days. Suction is then discontinued, and a semi-soft diet begun. After the first week, 30 cc. of mineral oil are given daily and oil enemas are employed where necessary. The patients are allowed to walk on the 12th postoperative day.

J. DUFFY HANCOCK.

BLACK, B. M., AND EVART, J. A. Nomenclature of certain gastric operations. Proc. Staff Meet. Mayo Clinic, 21: 229 (June) 1946.

The use of eponyms in scientific work is to be deplored, but in the case of gastric surgery the most descriptive and accurate way of representing the procedure involved is by use of the name of the originator or the popularizer of the operation. A brief historical sketch is given of the various well-known surgical procedures for resection of the stomach and their evolution, and particular emphasis is placed upon the Moynihan operation, which appears to be less well known than other operations on the stomach. The Billroth I operation, employing gastroduodenostomy, became the first classic standard. However, the modern forms of gastric resection stem from the Billroth II operation with antecolic gastro-jejunal anastomosis. Polya truly popularized and simplified this operation by joining the whole open end of the stomach to the jejunum as a retrocolic anastomosis. The Moynihan operation is like the Polya type in that the whole open end of the stomach is joined to the jejunum, but it utilizes an antecolic anastomosis in which the proximal portion of the jejunum is approximated to the greater curvature side of the stomach rather than to the lesser curvature side. Moynihan called it the "no loop" operation because it allows such a short segment of

jejunum between the ligament of Treitz and the site of the anastomosis.

FRANK NEUWELT.

PHYSIOLOGY: SECRETION

SCHONHEYDER, F., AND VOLQUARTZ, K.

The gastric lipase in man. *Acta Physiol. Scand.*, 11: 349 (June) 1946.

The majority of investigations on gastric lipase are rather ancient and have been carried out mostly with fats which were not well defined. In the present study, experiments were undertaken both *in vitro* and *in vivo*. The authors were able to show that gastric juice from adults and infants contains a characteristic lipase, which is identical with the lipase present in the gastric mucous membrane.

As in the case of pancreatic lipase, the optimum pH for gastric lipase is very dependent on the triglycerides used as a substrate, the optimum pH for the lower triglycerides being about 5.5 and for the higher triglycerides about 7.5. In case of the higher triglycerides, calcium chloride is able to shift the optimum pH to the acid side. The human gastric lipase is a very stable enzyme in acid medium. *In vivo*, only the lower triglycerides seem to be hydrolyzed to an appreciable degree by means of the gastric lipase, and apparently there is no basis for assuming that this enzyme plays a greater role in fat digestion in infants than in adults.

ALBERT CORNELL.

PHYSIOLOGY: MOTILITY

NECHELES, H., WALKER, L., AND OLSON, W. H. Effect of hemorrhage on gastro-intestinal motility of dogs: A gradient of gastro-intestinal motility. *Am. J. Physiol.*, 146: 449 (June) 1946.

Gastro-intestinal motility was recorded in unanesthetized dogs with chronic fistulae and in dogs anesthetized with pentobarbital sodium, morphine-barbiturate, or ether. Following a control period, varying amounts of blood were withdrawn. Following smaller hemorrhages which did not affect blood pressure materially, or following larger hemorrhages which lowered blood pressure considerably, the following observations were

made. The motility of the colon increased in most experiments, independent of the type of anesthesia used. The motility of the stomach, of the gastric antrum, and of the small intestine in most experiments either was not changed or was depressed; there was stimulation of motility in a number of experiments, but this depended on the type of anesthesia employed. In the response of the gastro-intestinal tract to hemorrhage, a distinct gradient effect was observed. It is believed that the stimulation of colonic motility by hemorrhage is not due primarily to the drop of systemic blood pressure.

ARTHUR E. MEYER.

METABOLISM AND NUTRITION

MARKS, M. M. Failure of lipid metabolism: Proctologic significance. *Southern Med. J.*, 39: 477 (June) 1946.

A constant feature of the acneic pyoderma here described was a hypercholesteremia, with titers ranging from 180 to 350 mg. per cent. It is believed that the diet offered by the Army, and the fatty foods selected by the patient, combine in the presence of hypothyroidism to produce the disease, wherein sebaceous material accumulates in the glands of the skin and acts as a foreign body in the development of inflammation. Since thyroid deficiency is manifested by low basal metabolic rate, low morning temperature, hypercholesteremia, and chronic fatigue, supplementary thyroid is given in sufficient quantity to produce clinical improvement. The dose is gauged by rise in the basal rate and in the morning temperature, as well as by subjective and objective response. The proper dose is a variable quantity, but more than 2 grains of thyroid U.S.P. daily in divided doses is rarely required. All patients are placed on low fat diets with adequate caloric intake of non-fatty foods. The purposes and methods of treatment are thoroughly explained to them, so that by co-operating they may adapt themselves as well as possible to their dietary opportunities. In a series of cases admitted to the septic and proctologic section of the surgical service of an Army hospital, 20% entered for treatment of chronic suppurative lesions of the skin due to some

form of acne. A constant clinical picture of inadequate thyroid activity and excessive ingestion of fats has been observed. Correction of diet, thyroid therapy, and adequate suitable surgical intervention are the therapeutic measures which have yielded success.

IRVING GRAY.

CARNEY, H. M. Wound healing with low vitamin C level. *Ann. Surg.*, 123: 1111 (June) 1946.

During the winter of 1943-1944 Carney had an opportunity to look for a relationship between plasma ascorbic acid levels and the rate of wound healing in soldiers fighting in the Italian mountains. He studied a group of 100 men who had a known diet. Their rations for a month or longer before hospital admission had a potential vitamin-C content of 60 to 70 mg. daily, entirely in the form of lemon powder. Only 2 men of the group had used the lemon powder consistently. Fourteen men took the powder sporadically, others not at all.

The plasma ascorbic acid levels of the 100 patients at admission varied between 0.1 and 2.35 mg.-% (70 were in the range of 0.2 to 0.5 mg.-%). Sixty-eight of the men had wounds; 8 of this number had interference in healing. Factors of debridement, immobilization, infection, plasma protein, and the general condition of the patient were related to wound healing. No relationship between wound healing and plasma ascorbic acid levels could be demonstrated.

LEMUEL C. MCGEE.

VILTER, R. W., WOOLFORD, R. M., AND SPIES, T. D. Severe scurvy. A clinical and hematologic study. *J. Lab. Clin. Med.*, 31: 609 (June) 1946.

Vilter and his colleagues review the clinical features of 19 patients with severe scurvy seen in the Cincinnati General Hospital from 1935 to 1945. The observations made were similar to those of other workers. Perifollicular hemorrhages, ecchymoses, swollen painful joints, and swollen blue-red tender gums occurred frequently. Blood pressures were low. Anemia occurred in 17 of the 19 patients; it was generally normo-

chromic and normocytic. Reticulocytosis, leukopenia, thrombopenia, and mild jaundice of the hemolytic type were common. Two patients improved clinically and hematologically after bed rest, although kept on a diet restricted in vitamin C. In 9 others, such change resulted only after the administration of crystalline vitamin C.

The authors believe that the conflicting reports on scorbutic anemia can be explained by the concept of the presence of a multiple deficiency state, with many factors beside vitamin C affecting the bone marrow; however, they state that the anemia in their 11 cases occurred primarily because of vitamin C deficiency.

EDGAR WAYBURN.

BRANSBY, E. R. The diets of families with children in 1941. *Brit. Med. J.*, 4456: 832 (June) 1946.

A dietary survey was made in 1941 of 849 families in 8 localities in England and Scotland. Despite rationing and the introduction of the National milk scheme in this year, there were wide differences in the consumption of foods and the nutritional adequacy and palatability of the diets consumed by families when grouped according to food expenditure per person. Particularly low, according to the standards adopted, were the intakes of calcium, vitamin A, and ascorbic acid; despite this, there was no evidence of a prevalence of clinical signs of ascorbic acid deficiency throughout the country.

The consumption of most foods, and especially protective foods, was considerably greater among families with high than among those with low food expenditure per person. The intake of all nutrients, except protein, was inadequate among the groups with food expenditures of less than about 9 shillings per person per week; the calcium intake was inadequate among all groups, irrespective of the level of food expenditure. Data are presented on the types of meals eaten by persons of different ages in the various food expenditure groups. It is shown that the diets of the poor families were much less varied than those of well-to-do families.

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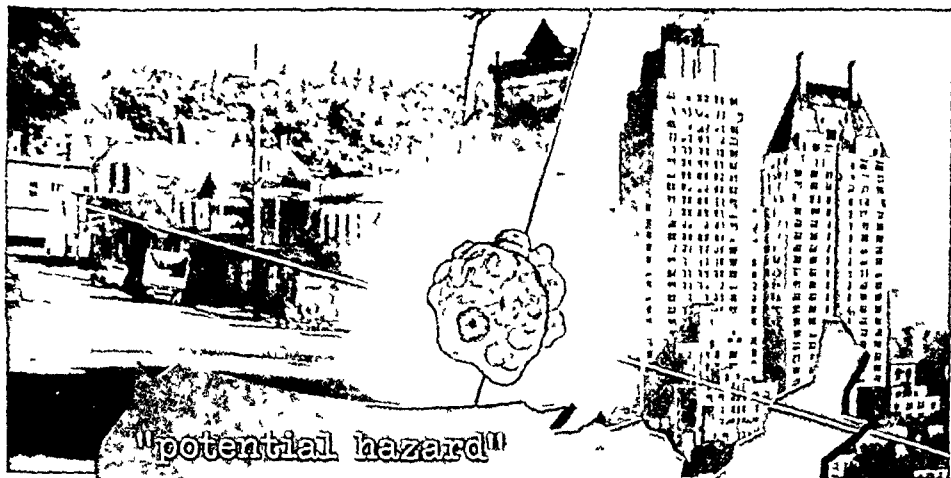
CRILE, G., JR., AND JAFFE, H. L. Pancreatic calculi as a rare cause of intestinal hemorrhage. *Radiol.*, 46: 586 (June) 1946.

A case in which pancreatic calculi formed a fistula leading into the second portion of the duodenum is reported. The mouth of this fistula had the appearance of a chronic

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- Meleney, H.E. - Am. J. Pub. Health, 34:20 (Jan.) 1944.

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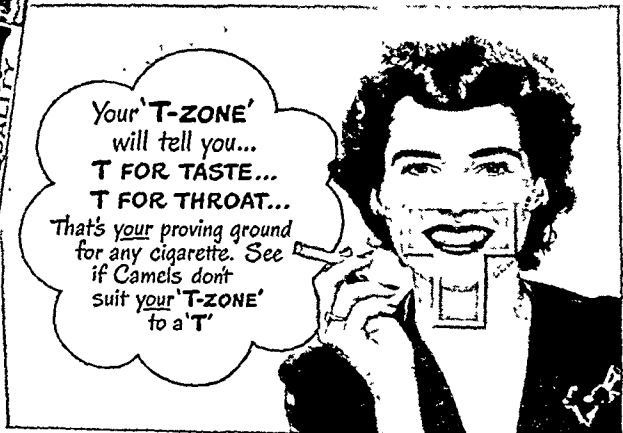
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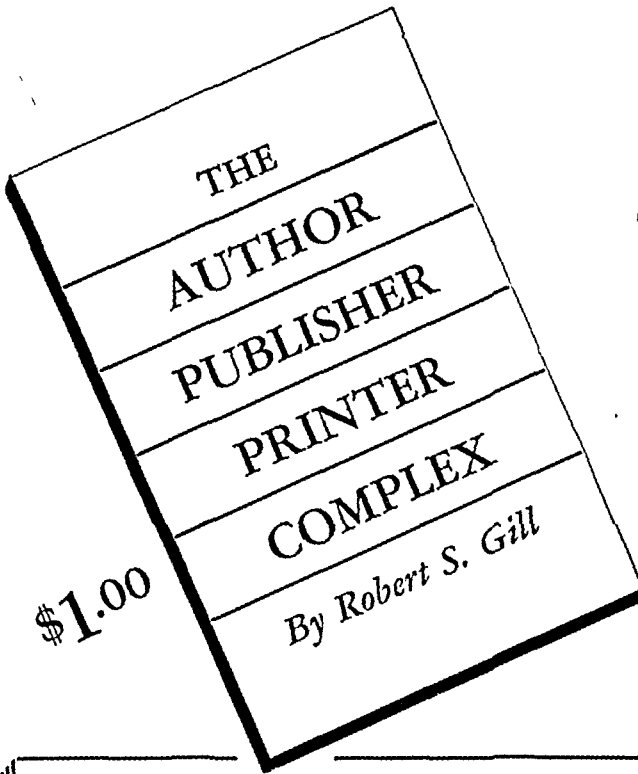
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¹ Amer. J. Med. Sci. 211, 513 (May, 1946).

² Ibid. 212, 179 (August, 1946).

³ J. Clin. Invest. 24, 278 (May, 1945).

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Official Journal of the American Gastroenterological Association

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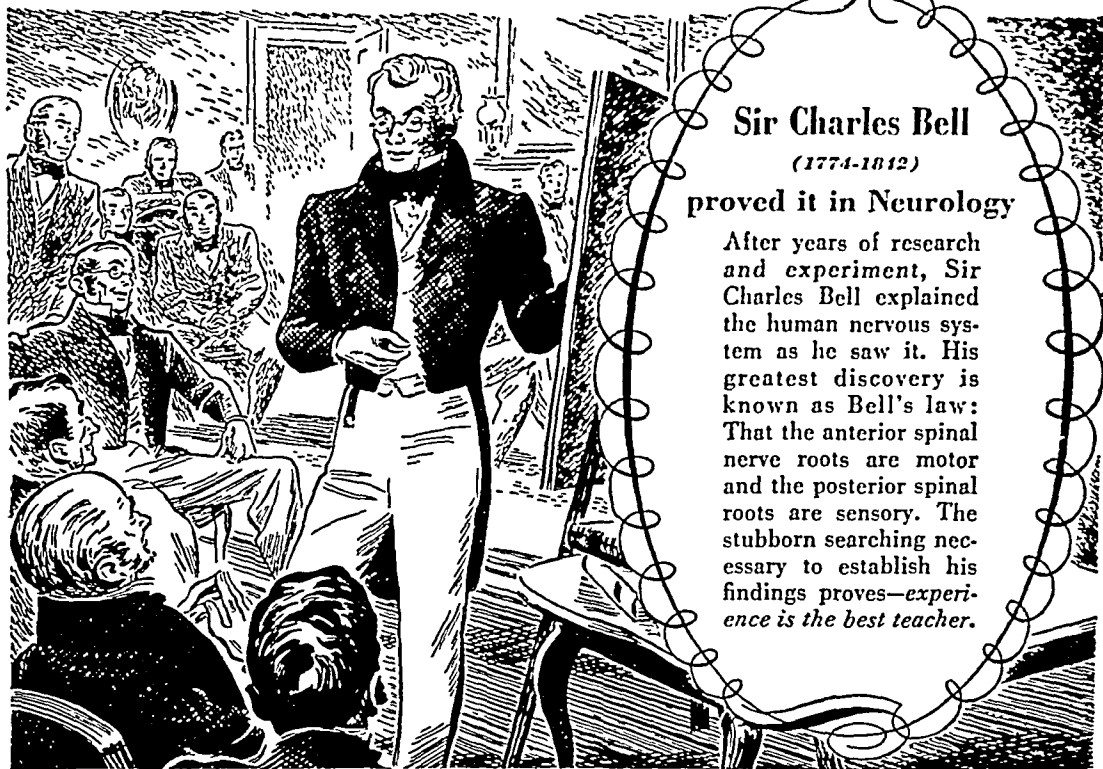
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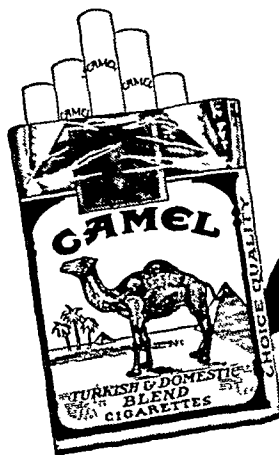
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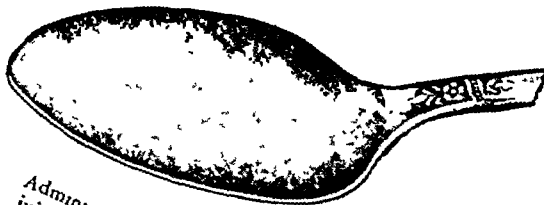
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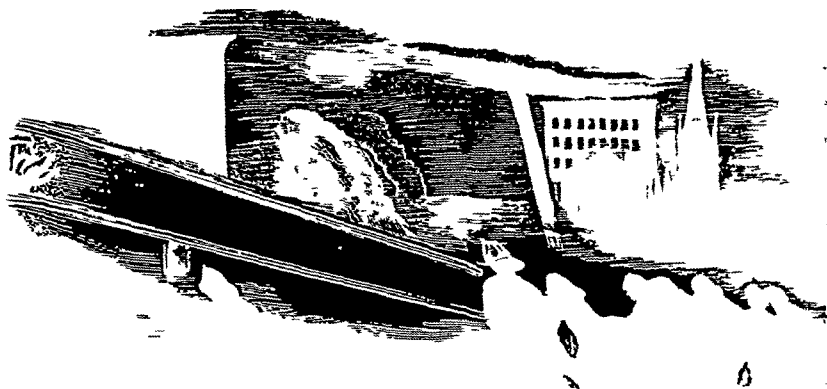
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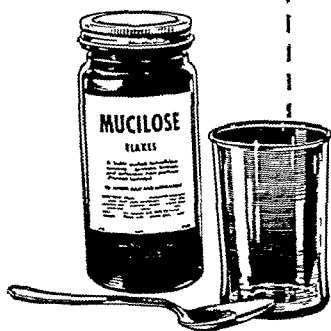
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GASTROENTEROLOGY

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VOLUME 8

March 1947

NUMBER 3

THE LIMITATIONS OF ROENTGENOLOGY AND GASTROSCOPY IN THE DIAGNOSIS OF DISEASES OF THE STOMACH: AN ANALYSIS OF FIFTY-THREE PROVEN CASES*

EDWARD B. BENEDICT, M. D.

From the Massachusetts General Hospital, Boston

INTRODUCTION

Although in the early days of gastroscopy there were many skeptics, everyone who has had close association with a competent gastroscopist for a reasonable length of time has learned to have confidence in his reports. The method has now spread to include almost every hospital or city of any size in this country and in many foreign countries. Many doctors returning from overseas are eager to learn gastroscopy. Gastroenterologists are coming to feel that direct inspection of the gastric mucosa by gastroscopy is an important adjunct to other methods of examination. Roentgenologists in most cases have been particularly glad to welcome an additional method of examining the stomach—a method which they realize is a supplementary and not a rival procedure.

Gastroscopy, however, should not be done routinely but should be reserved for certain cases where the clinician or roentgenologist is in doubt. I refer particularly (1) to borderline cases where the question of medical versus surgical treatment arises, (2) to cases where symptoms persist but x-ray studies are negative, and (3) to cases of unexplained gastrointestinal hemorrhage. In every case gastroscopy must be evaluated with the history, physical examination, x-ray study and laboratory work. Undue emphasis on any of these may lead to unfortunate results.

The writer (1) has recently reported 245 proven cases of gastric disease where there was complete data on gastroscopic, x-ray, and pathological findings. There were 125 carcinomas, 50 benign gastric ulcers, 25 duodenal ulcers, 8 jejunal ulcers, 16 gastritis, 7 benign tumors, 5 lymphomas, 2 sarcomas, 3 metastatic carcinomas, and 4 normal stomachs. In the detailed analysis of these cases, it was evident that both methods have their limitations. Although it is unfair to compare the roentgen examination with gastroscopy, since the latter supplements the former and is in no way competitive, it can be stated that in certain instances the roentgen ray examination appears to be superior

*Presidential address, The American Gastroscopic Club, Atlantic City, N. J., May 26, 1946.

to gastroscopy and in other cases gastroscopy seems to be superior to the roentgen ray. The roentgen examination and gastroscopy were about equal in 54 per cent of the cases. Roentgen examination was superior in 29 per cent, gastroscopy in 16 per cent. The chief causes of failure in gastroscopy are mechanical. If the gastroscopist can get a satisfactory view of the lesion, his chances of reaching a correct diagnosis seem to be greater than those of the radiologist. Greater diagnostic accuracy is attainable when both methods are used cooperatively than when either method is used alone.

The present study on the limitations of gastroscopy and radiology in the differential diagnosis of benign and malignant lesions of the stomach is based on an additional series of 53 cases of proven gastric disease namely, 19 carcinomas, 21 benign gastric ulcers, 2 jejunal ulcers, 5 gastritis, 2 benign tumors, 1 lymphoma, 1 normal posterior gastroenterostomy stoma, and 2 normal stomachs. The much higher incidence of gastric resection for benign ulcer in the present series than in the first series may be an indication of the increased tendency on the part of the hospital staff to be unwilling to treat gastric ulcer medically. Another factor, however, must be considered, namely, that when gastric carcinoma is fairly obvious by x-ray examination, gastroscopy should not be performed as frequently as it has been in the past.

CARCINOMA

In the 19 proven carcinoma cases, x-ray and gastroscopy were both correct in 10 instances. They were both incorrect in only one case. In this discussion, we are interested in the limitations of both methods, and, therefore, will not discuss the cases where both methods were correct.

One Case Illustrating the Limitation of Both X-ray and Gastroscopy in Carcinoma

J. F. In this case, the radiologist reported a large ulcer crater irregular in outline measuring 3.5 x 2 cm. in diameter immediately below the cardia in the upper portion of the fundus of the stomach and surrounded by an area of infiltration. The duodenal cap was constantly deformed, irregular in outline, but without demonstrable crater. The findings were those of a gastric ulcer probably benign and active, and a duodenal ulcer probably inactive. Four days later, the gastroscopist reported an ulcerating lesion in the same area with a grey base and sharp margins. There was no nodular appearance, no rigidity and no irregularity. The findings were consistent with a benign gastric ulcer. A few days later this lesion was resected. The pathological report was adenocarcinoma, grade II.

Comment: Although the radiologist's description of a large ulcer crater irregular in outline makes one think of carcinoma, he said in his conclusions that the ulcer was probably benign. The gastroscopist also felt that the lesion was probably benign. Both were wrong, but the correct procedure was undertaken namely, surgical resection.

Two Cases Illustrating the Limitation of Gastroscopy in Carcinoma

E. G. The radiologist examined this patient four times over an eight-month period and reported: (1) a small gastric ulcer which had already undergone considerable healing: (2) apparent healing of the gastric ulcer: (3) (seven months later) "I cannot be at all sure that this lesion has ever healed and the usual feelings regarding a gastric ulcer must be kept in mind. The ulcer is definitely larger than at any time in the past." (4) (six weeks later) the ulcer was, if anything, a little bit

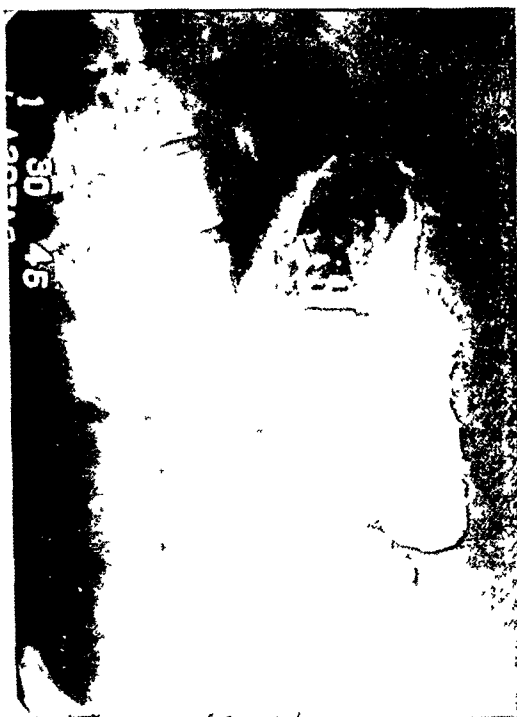


FIG. 1. E. G. X-RAY APPEARANCE OF PROVEN SIGNET RING CELL CARCINOMA TWO WEEKS BEFORE RESECTION

Chiefly because of increasing size after four x-ray observations during an eight months' period the radiologist was suspicious of carcinoma. The gastroscopist made only one examination and felt that grossly the lesion was benign.

larger than at the previous observation (fig. 1). Gastroscopy was performed only once (shortly before the last x-ray examination), and a lesion 1 cm. in diameter was found high up on the lesser curvature close to the cardiac orifice with sharp red margins and a clean grey base surrounded by considerable reddening and edema. No nodular or irregular appearance was noted. The findings were consistent with a benign gastric ulcer. Microscopic malignancy could not be excluded. The stomach was resected one month after the gastroscopic examination and two weeks after the last x-ray examination. The pathological report was signet ring cell carcinoma.

Comment: In this case, the radiologist had the advantage of making four examinations and even then was quite doubtful about the nature of the ulcer. The gastroscopist judging only by the gross appearance at a single examination felt the lesion was benign, but all concerned felt that an unhealed gastric ulcer observed for about nine months should certainly be operated upon.

P. G. X-ray examination demonstrated a 1 x 1.5 cm. ulcer 2.5 cm. proximal to the pylorus on the lesser curvature. This certainly had the appearance of an ulcer probably in a carcinoma of the antrum. Two days later, the gastroscopist failed to



FIG. 2. W. H. X-RAY FILM OF GASTRIC LESION DESCRIBED BY THE RADIOLOGIST AS GROSSLY BENIGN

The gastroscopic appearance, however, was that of carcinoma. The pathological report was carcinoma. See fig. 3.

visualize the lesion described by x-ray. The angulus appeared normal. A normal peristaltic wave was seen passing over a normal appearing antrum to a tight closure at what appeared to be normal pylorus. No ulcer was visible. Three days later a subtotal gastrectomy was performed, the pathological report being adenocarcinoma, grade III. There was also a lipoma of the stomach close to the carcinoma.

Comment: Gastroscopy failed to visualize this lesion which was well described by x-ray and which was found at operation and confirmed pathologically. The only explanation must be that what appeared to be the pylorus was actually a prepyloric contraction proximal to it.

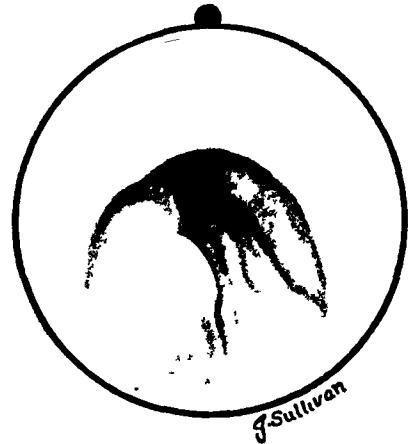
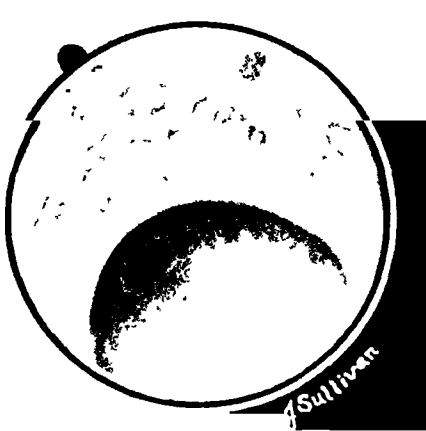
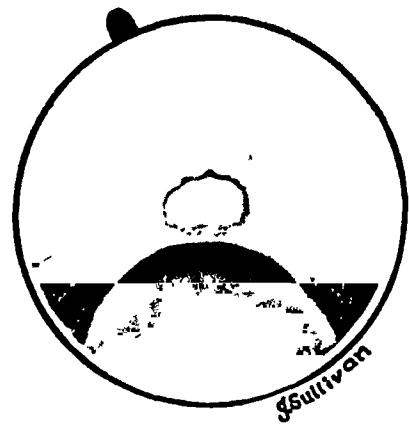
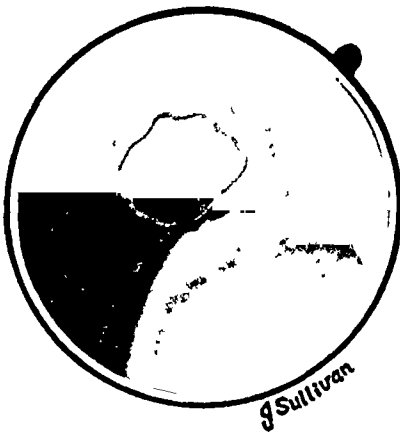


FIG 3 (UPPER LEFT) W. H. GASTROSCOPIC VIEW OF LESION SHOWN BY X-RAY IN FIG. 2

The gastroscopist described the lesser curvature of the angulus as being irregular and nodular merging into an ulcer crater about 2 cm. in diameter with nodular irregular margins. The appearance was that of carcinoma. The pathological report was carcinoma

FIG 6 (UPPER RIGHT) J. A. GASTROSCOPIC VIEW OF ULCER SHOWN BY X-RAY IN FIG. 5

This was erroneously thought to be carcinoma by the gastroscopist. Compare with similar appearance shown in fig. 3 where the lesion was malignant.

FIG 8 (CENTER LEFT) D. B. GASTROSCOPIC VIEW OF GASTRITIS DISCUSSED UNDER FIG. 7

FIG. 9 (CENTER RIGHT) T. H. BENIGN SUBMUCOSAL LEIOMYOMA AS SEEN THROUGH THE GASTROSCOPE

FIG. 10 (LOWER LEFT) B. D. GASTROSCOPIC APPEARANCE OF MULTIPLE SMALL POLYPS CONFIRMED PATHOLOGICALLY BUT NOT VISIBLE BY X-RAY

FIG. 11 (LOWER RIGHT) H. J. PROVEN LYMPHOMA AS SEEN BY GASTROSCOPY

The gastroscopist was positive about severe gastritis and erosions and was very suspicious of lymphoma. See text

Six Cases Illustrating the Limitations of X-ray in Carcinoma

W. H. Three x-ray examinations were performed. The first radiologist described a large ulcerated lesion on the lesser curvature wall of the stomach probably malignant. The second radiologist (three weeks later) reported an ulcer crater 2 cm. in diameter and 1.5 in depth grossly benign. Two weeks later, a third radiologist reported practically no change in the size and appearance of the previously described gastric ulcer (fig. 2). Four days after the last x-ray examination, the gastroscopist reported that with the indicator in the two o'clock position the angulus was well seen. Its lesser curvature margin appeared irregular, red, edematous and nodular merging into an ulcer crater which appeared about 2 cm. in diameter and 1 cm. deep with definitely nodular irregular margins but with a rather clean base occupied by mucus (fig. 3). The surrounding mucosa was red, indurated, edematous and appeared rigid on air inflation. The normal peristaltic wave did not begin at the angulus as it usually does but the angulus remained open and a short wave seemed to pass normally over the distal antrum. No abnormality was noted in the distal antrum or pylorus except for reddening. Throughout the body of the stomach there was marked reddening, edema and adherent secretion with some areas of verrucous appearance. The induration surrounding the ulcer extended along the lesser curvature for 2 or 3 cm. above the lesion. The gastroscopic appearance was that of carcinoma. Two weeks later, gastric resection was done, the pathological report being carcinoma.

Comment: Although the first radiologist reported the large ulcer was probably malignant, two subsequent radiologists described the lesion as grossly benign. The gastroscopic appearance, however, was definitely that of carcinoma.

J. M. The radiologist demonstrated thick folds in the mid portion of the stomach particularly along the greater curvature with increase in the rigidity of the stomach in this area. The lesser curvature did not appear rigid but was apparently involved in the process. In the central portion of this area no folds could be demonstrated, apparently due to the large ulcer. The antrum appeared normal. The upper edge of the lesion was not clearly delineated, but reached close to the cardia. The appearance was that of an ulcerated tumor, question of cancer, question of lymphoma. The gastroscopist found on the greater curvature of the angulus a sloughing, nodular lesion extending from this point along the greater curvature for a distance of about 7 to 10 cm. The lesion was ulcerating, nodular and sloughing with raised margins and a tongue-like mass projecting toward the cardiac end. It appeared to be about 4 cm. in width. On the lesser curvature of the antrum, there was a rounded smooth submucosal elevation about 1.5 cm. in diameter suggesting possible further infiltration of the lesion. The findings were characteristic of a nodular, ulcerating carcinoma of the greater curvature of the stomach with superficial gastritis. It was believed that there was enough normal stomach above the lesion to enable resection. The pathological report was adenocarcinoma, grade III with metastases to regional nodes.

Comment: The radiologist in this case raised the question of lymphoma, but to the gastroscopist this was very definite carcinoma. The proximal margin of the lesion also seems to have been somewhat better defined by the gastroscopist.

L. C. X-ray examination was done at an outside hospital by a very experienced radiologist who made at least two examinations,—the first of which was suggestive of some infiltration along the lesser curvature, but on the second examination there was no evidence of defect. Gastroscopy was performed three days later at which time the angulus was constantly distorted by a rounded elevated mass about 1 cm. in diameter on the lesser curvature. With the indicator in the twelve o'clock position, a sluggish peristaltic wave was seen to pass apparently with difficulty down the antrum but the deformity remained and other slight irregularities of the contraction wave appeared. The antrum appeared to be slightly rigid and tubular. The wave could not be followed quite to the pylorus. Above the angulus on the lesser curvature and toward the posterior wall, there was some increased reddening and a somewhat rigid slightly indurated appearance. One month later, a subtotal gastrectomy was performed, the pathological report being adenocarcinoma, grade III. The tumor was reported as infiltrating the mucosa widely and might possibly extend to the proximal resection edge along the lesser curvature. The regional lymph nodes were not involved.

Comment: In this case, the radiologist although suspicious of a possible malignancy was doubtful. The gastroscopist, however, was very definite in his report.

E. G. Here the radiologist demonstrated an irregular ulceration at the angle of the stomach on the lesser curvature 3 cm. in length and 2 cm. in width. There was another irregular smaller ulceration above it, and a questionable even smaller ulceration below it. The whole area was rigid and surrounded by a margin of infiltration. In spite of this description, he was unable to decide the question of the nature of the ulcerations from the x-ray examination. Malignancy was a distinct possibility. Eight days later, the gastroscopist found on the lesser curvature at the angulus a nodular ulcerating mass extending into the antrum for a distance of 3 or 4 cm. Peristalsis was sluggish and failed to pass over this area. Because of the rigidity, it was impossible to balloon out the antrum in the usual manner. The findings were those of carcinoma of the lesser curvature of the stomach with some superficial gastritis. Five days later, a subtotal gastric resection was performed. The pathological report was scirrhus carcinoma.

Comment: Here is another case in which the radiologist was doubtful, but the gastroscopist was very definite.

J. L. X-ray examination demonstrated that the greater curvature side of the body of the stomach had a somewhat rigid appearance on the films but this was not definite fluoroscopically. No ulceration or tumor mass was seen. The findings were suggestive of the possibility of pathology along the greater curvature side of the stomach either extrinsic or intrinsic. This, however, was not entirely definite. One week later, gastroscopy was performed. The lesser curvature of the angulus appeared slightly irregular. Normal active peristalsis was seen starting at the angulus and passing down over what appeared to be normal antrum to a tight closure

at what appeared to be normal pylorus. Proximal to the angulus the mucosa was red and edematous with huge rugae especially on the greater curvature. Some of the rugae had nodules on their crests and presented erosions and ulcerations. With the indicator in the seven o'clock position on the greater curvature, there was a cauliflower-like irregular mass about 2 cm. in diameter of a yellowish-gray color. It was impossible to inflate the stomach adequately with air, the impression being that of rigidity. The lesser curvature was not as well seen as usually because of inadequate inflation. This also presented an indurated red, edematous, rigid appearance. This appearance extended well up to the cardiac orifice on the lesser curvature where there was reddening, edema, adherent secretions, and erosions. The findings were consistent with ulcerating, eroding, infiltrating carcinoma involving a very large part of the body of the stomach. Lymphoma was considered a possibility but much less likely. The examiner did not believe that gastritis alone could produce that picture. Transthoracic total gastrectomy was performed. The pathological report was adenocarcinoma, grade III with metastases to regional lymph nodes.

Comment: In this case, the radiologist was unable to decide whether there was an extrinsic or intrinsic lesion involving the stomach. By gastroscopy, however, the gastric tumor was very definite.

T. L. The radiologist reported on the lower half of the greater curvature side of the stomach a lesion which appeared 8 cm. in length. The wall of the stomach was irregular and somewhat rigid in this area and no peristalsis was seen to pass. The findings were those of a lesion involving the greater curvature of the stomach and were thought to be possibly due to a localized area of gastritis but could well have been due to malignancy. Gastroscopy was performed four weeks later and showed the angulus somewhat distorted and even with inflation did not present the usual round appearance. A curtain of inflammatory or neoplastic tissue hung down from the lesser curvature. Peristalsis was absent. A large part of the body of the stomach was occupied by an irregular, ulcerating, sloughing, partly proliferating, mass consistent in appearance with carcinoma. This was visible in the lower part of the body of the stomach with the indicator in the nine o'clock position. The lesion extended from the angulus apparently to within about 2 cm. of the cardiac orifice. There was an old blood clot and some fresh blood in the stomach with some secretion. The findings were those of extensive carcinoma of the stomach with superficial gastritis. Gastrectomy was performed about a week later. The pathological report was adenocarcinoma, grade III.

Comment: Here is another case in which the radiologist suspected malignancy but was not quite sure. The gastroscopist had no doubt about the diagnosis of carcinoma.

In discussing these 19 proven carcinoma cases, it is only fair to say that x-ray examination is always performed before gastroscopy, and the latter is not usually indicated when the diagnosis of carcinoma is obvious by x-ray. Gastroscopy is used to confirm a difficult diagnosis and to supplement x-ray examination in doubtful cases. It may also aid in defining the extent of a

lesion. Gastroscopy is thus an extremely valuable adjunct to x-ray examination but is definitely not a substitute for it. If the situation were reversed, that is if gastroscopy were easier to do than x-ray examination and were done first, the gastroscopist would probably be in doubt on many occasions and would then call upon the roentgenologist to help him out. It is really extremely interesting and satisfying in spite of the limitations of both methods to see how frequently one supplements the other.

BENIGN GASTRIC ULCER

Twenty-one cases fall into this group of pathologically proven benign gastric ulcer. In only eight of these were the radiologist and gastroscopist both correct, and in five both were incorrect. This compares unfavorably with the carcinoma group where in nineteen cases both methods were correct in nine instances but incorrect only once. A partial explanation for the greater accuracy of both methods in carcinoma is that in benign ulcer there may be (1) an apparent nodularity due to severe gastritis surrounding the ulcer and leading to an erroneous diagnosis of carcinoma; (2) an unusual amount of rigidity in the area of a benign ulcer which makes one suspect a carcinoma; (3) a desire on the part of both the radiologist and the gastroscopist to prefer to err on the side of carcinoma.

Five Cases Illustrating the Limitation of Both X-ray and Gastroscopy in Benign Ulcer

E. G. In this case the x-ray report was as follows: "the stomach showed some narrowing in its middle one-third and on the greater curvature at this point there was an area of ulceration measuring 1.8 cm. in diameter by 1 cm. in depth. There was some thickening of the gastric wall about the crater but there was very little disturbance in the mucosal pattern. The lower stomach, duodenal cap and loop were not remarkable. The findings were those of an ulcerating lesion probably malignant at the mid point on the greater curvature of the stomach." On gastroscopy the angulus was constantly deformed by two ulcerations. One was rather shallow, toward the lesser curvature, about 1 cm. in diameter with a clean whitish-gray base and sharp margins, the other ulcer toward the greater curvature was apparently about 1 cm. deep and about 1.5 cm. in diameter with raised crater-like margins. The base was not visible. No peristalsis was present, and the deformity was constant. Proximal to the greater curvature ulcer on the posterior wall, the mucosa was nodular and cobblestoned. There was some mucosal hemorrhage, a considerable amount of reddening and edema and a superficial ulceration about 1 mm. deep and 2 cm. x 1 cm. in diameter on the greater curvature in the mid portion of the body with slightly reddened margins. Other erosions were also visible. With considerable air inflation, a few blood vessels were visible. The findings were those of superficial and hypertrophic gastritis with multiple erosions and ulcers. The gastroscopist felt that surgery was definitely indicated and that the condition was probably malignant. His first choice was lymphoma, second choice carcinoma, third choice multiple benign

ulcers. Gastric resection was performed. The pathologist reported benign gastric ulcer, severe acute and chronic gastritis with gastric atrophy.

Comment: In their diagnosis of malignancy, the radiologist and gastroscopist were both probably influenced by the fact that the ulcer was located on the greater curvature and that such ulcers are almost always malignant. The gastroscopist seriously considered the diagnosis of lymphoma because of the unusual appearance, the severity of the gastritis, the very marked cobblestone appearance, and the multiplicity of the ulcerations and erosions. The gastroscopist reported severe superficial and hypertrophic gastritis, but the pathologist found in addition severe atrophy. The patient is only twenty-nine years old and is apparently the "exception that proves the rule" with regard to greater curvature ulcers being one hundred per cent malignant.

J. M. X-ray examination showed that the barium after passing through the cardia immediately entered a large crater approximately 2 cm. in diameter in the region of the fundus. There was a filling defect adjacent to the crater and rigidity of this area. The remainder of the stomach was not remarkable. The findings were those of an ulcerating lesion in the fundus of the stomach which had the appearance of carcinoma. The gastroscopist described a slightly nodular elevated appearance just inside the cardiac orifice on the lesser curvature. The appearance was consistent with neoplasm. It was felt, however, that a thick fold could produce a similar picture but would be unlikely in that area. A transthoracic partial gastrectomy was performed, the pathological report being gastric ulcer.

Comment: Neither method of examination reached the correct diagnosis in this case. X-ray examination revealed a definite ulcer which was thought to be malignant. The gastroscopist apparently did not see the ulcer but thought the surrounding area was sufficiently nodular to be consistent with carcinoma.

P. M. Barium examination of the stomach revealed an ulcer crater measuring 1.5 cm. across the base by about 1 cm. deep on the lesser curvature of the stomach about 7 cm. below the cardia. Around this there was a somewhat flattened filling defect for a distance of approximately 8 cm., the appearance being best explained on the basis of an ulcerating carcinoma. The possibility of a leiomyosarcoma was considered. The radiologist did not believe it was a benign ulcer and advised gastroscopy. The gastroscopist reported that the mucosa throughout the antrum and body showed increased reddening with edema and adherent secretion. With the indicator in the nine o'clock position high up on the lesser curvature toward the anterior wall, there was an ulcerating lesion about 2 cm. in diameter with slightly irregular nodular margins. The elevated nodular appearance surrounding the ulcer seemed to extend about 6 to 8 mm. and was very close to the cardiac orifice. The findings were consistent with carcinoma of the lesser curvature and anterior wall close to the cardiac orifice with superficial gastritis. A transthoracic resection of the stomach was performed, the pathological report being active benign gastric ulcer, with acute and chronic gastritis.

Comment: Here again the inflammatory appearance surrounding the benign ulcer led to the erroneous x-ray and gastroscopic diagnosis of ulcerating carcinoma.

J. M. X-ray examination (fig. 4) in this case disclosed a 3 x 2.5 x 2 cm. crater on the posterior wall and lesser curvature of the stomach just below the cardia, the lesion appeared to be in a filling defect, the upper margin of which was somewhat shelf-like. The remainder of the stomach showed rather small peristaltic waves, although there was some stiffness without definite evidence of rigidity except for about 3 cm. below the lower margin of the lesion. The findings were those of an

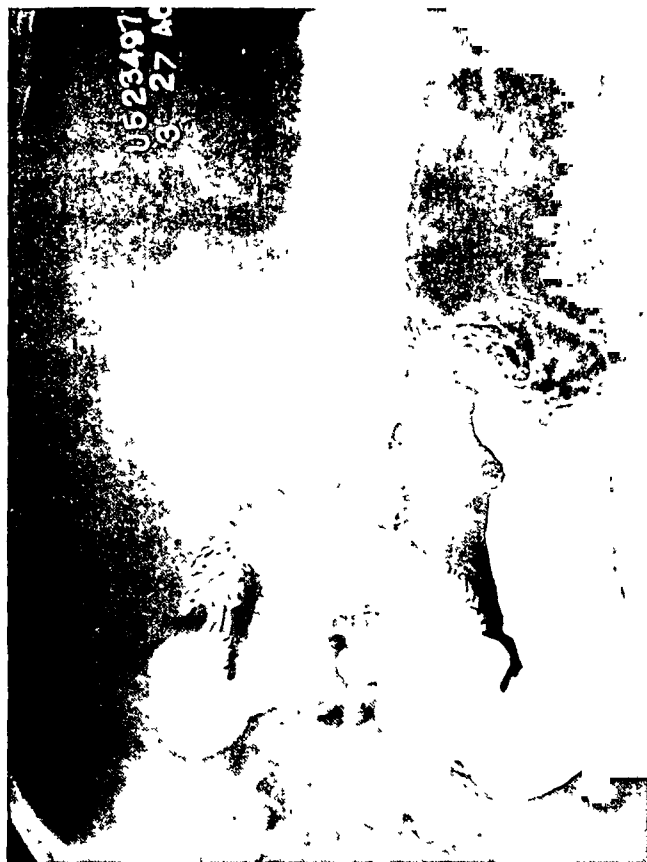


FIG. 4. J. M. X-RAY FILM SHOWING A 3 x 2.5 x 2 CM. CRATER ON THE POSTERIOR WALL OF THE LESSER CURVATURE OF THE STOMACH JUST BELOW THE CARDIA

The lesion appeared to be in a filling defect, the upper margin of which was somewhat shelf-like. The radiologist favored carcinoma: the gastroscopist also favored carcinoma because of the irregular margins of the ulcer. The pathological report, however, was active gastric ulcer with chronic gastritis.

ulcer in the region of the cardia of the stomach involving the lesser curvature and posterior wall. The most likely diagnosis would seem to be carcinoma. Gastros-copy was then performed, the gastroscope meeting complete obstruction at the cardiac orifice. With the omniangle mirror in the foroblique position, it was possible to see through the cardiac orifice into the stomach where on the lesser curvature there was visible a 3 cm. ulcer crater with slightly irregular margins. The base of the crater was sloughlike. From the gastrosopic appearance it was felt to be probably ma-

lignant. The failure of the gastroscope to pass the cardiac orifice was also thought to be in favor of malignancy. A transthoracic partial gastrectomy was performed, the pathological report being active gastric ulcer with chronic gastritis.

Comment: Here is another example of how impossible it is in some cases to differentiate benign gastric ulcer from malignant gastric ulcer. Although both the radiologist and gastroscopist were somewhat doubtful, both favored malignancy. Failure of the gastroscope to pass the cardiac orifice may be due to carcinoma or to benign ulcer with spasm. The use of the omniangle mirror in the foroblique position permitted a view of this lesion which could not have been obtained with the usual right angle vision.

J. P. X-ray examination disclosed considerable rigidity throughout the prepyloric area particularly along the lesser curvature side with an ulcer-like projection at the angle of the stomach where the rigidity started. This region was tender on palpation and no peristalsis was seen to pass over this area. The findings were quite suggestive of a carcinoma at the region of the antrum of the stomach. The gastroscopist reported a normal angulus. The peristaltic wave began normally with a circular appearance in the angulus but as it proceeded down the antrum there was a constant gothic arch deformity toward the lesser curvature and anterior wall. No ulcer or carcinoma could be seen. The pylorus, however, was only partially seen and the lesser curvature in the immediate prepyloric area could not be satisfactorily visualized. Before the examination was completed, the gastroscopic light went out and the examination was discontinued. The gastroscopic findings were inconclusive, but there seemed to be some deformity in the distal part of the antrum. A subtotal gastrectomy was performed, the pathological report being active benign gastric ulcer.

Comment: Neither the radiologist nor the gastroscopist could be certain of the pathology of this case. The radiologist described an ulcer-like projection with rigidity, which he thought was probably carcinoma. The gastroscopist described a deformity but could not positively see the lesion. On the whole, the x-ray examination was more helpful in this case than the gastroscopy, but neither method resulted in a correct pre-operative diagnosis. The limitation of the gastroscope in this case was partly mechanical inability to visualize a relatively blind area of the stomach and difficulty with the gastroscope light (a very rare accident) before the examination was completed.

Six Cases Illustrating the Limitation of Gastroscopy in Benign Gastric Ulcer

J. A. The radiologist reported the lesser curvature was shortened and somewhere along it, probably in the lower third, there was an ulcerating lesion measuring about 1 cm. in depth and 1.5 cm. across (fig. 5). Definite tumor could not be found in this region, but neither could it be ruled out. There was antral spasm and evidence of old duodenal ulcer. The shortening of the lesser curvature of the stomach was felt to be in favor of a benign ulcer. Three days later gastroscopy was performed disclosing a constant gothic arch deformity of the angulus in the twelve o'clock position. Peristalsis was absent. After several minutes the antrum which had been in

slight spasm relaxed sufficiently to permit a good view of an ulcer on the lesser curvature just beyond the angulus approximately 1 cm. in diameter and almost circular with a rather dirty base but sharp, smooth edematous margins. The findings were consistent with benign ulcer of the lesser curvature of the stomach with moderately severe superficial gastritis. Microscopic malignancy could not be excluded. This patient was given about three weeks trial of medical management after which re-examination of the upper gastrointestinal tract by x-ray showed the previously described ulcer close to the angle of the stomach slightly smaller than on the last



FIG. 5. J. A. X-RAY APPEARANCE OF ULCERATING LESION CONSIDERED BENIGN BY THE RADIOLOGIST AND PROVEN BENIGN PATHOLOGICALLY

The gastroscopist erred in considering this probably malignant. See fig. 6

examination. The radiologist's findings were those of benign gastric ulcer, but he felt that he could not rule out the possibility of malignancy. Four days later gastroscopy (fig. 6) was repeated revealing an ulcer which looked a little bigger and slightly more irregular with more nodular margins than at the previous examination. It was felt to be probably malignant. Resection was advised and performed, the pathological report being active gastric ulcer.

Comment: In this case, the radiologist was correct in finding a benign ulcer. The gastroscopist was incorrect in calling it probably malignant.

C. C. X-ray examination showed an ulcer projecting about 1 cm. beyond the lumen of the lesser curvature with a base 2.5 cm. in diameter on the lesser curvature side just below the cardia having the appearance of a grossly benign ulcer high up in the stomach. Gastroscopy was then performed and the gastroscope met with complete obstruction at the cardiac orifice. The ulcer was not visible.

Comment: In this case the failure of the gastroscopist to visualize the lesion was due to mechanical reasons.

J. L. X-ray examination showed high along the lesser curvature an ulceration measuring 4.5 cm. in the greatest diameter by 2 cm. in depth. It was surrounded by an area of rigidity and edema, 9 cm. in diameter. There was no definite evidence of tumor, but it was felt by the radiologist that an ulceration of this size should be regarded with some suspicion. The findings were those of a large gastric ulcer. Gastroscopy was then performed showing the upper half of the lesser curvature markedly reddened and edematous. The ulcer could not be brought into view. There was no nodular appearance demonstrable. The gastric wall along the lesser curvature did not appear rigid when air was introduced into the stomach.

Comment: X-ray examination in this case revealed a definite gastric ulcer which was not visible by gastroscopy. The upper part of the lesser curvature is a difficult place to see because the objective lens lies so close to the mucosa in that area. The gastroscope devised by Hermon Taylor of London is equipped with a ratchet on the proximal end enabling control of the flexible part of the gastroscope. One of the advantages claimed for this instrument is to permit a better view of the upper part of the lesser curvature. The writer has now used it often enough to believe that claim is probably true. If it had been used in the above case, the ulcer might have been visualized. This is another instance of mechanical failure of the usual type of flexible gastroscope.

H. N. The radiologist reported a large grossly benign gastric ulcer high up on the lesser curvature 2 cm. in diameter, 3 cm. in depth. The gastroscopist in this case was not able to visualize the ulcer. Several subsequent x-ray examinations over a period of three months showed almost complete healing of the ulcer with, however, a residual 2 mm. ulcer on the lesser curvature below the cardia surrounded by considerable swelling and radiation of the mucosal folds. A subtotal gastrectomy was performed, the pathological report being chronic gastritis with erosions.

Comment: The radiologist was undoubtedly correct in his diagnosis of an almost completely healed gastric ulcer which was not visible by gastroscopy. Here again the Hermon Taylor flexible gastroscope might have given a satisfactory view of the lesion.

E. F. X-ray examination was done on ten occasions over a period of three years showing on almost every occasion a gastric ulcer on the lesser curvature in various stages of activity from a large ulcer to complete healing, but always apparently grossly benign. Gastroscopy was done four times during this period with the following diagnoses: (1) question of healing gastric ulcer with gastritis, question of malignancy: (2) (two weeks later) normal appearing stomach: (3) (two and a half years later) no ulcer visible, marked acute superficial gastritis: (4) (one week later)

ulcer not visible, severe superficial and hypertrophic gastritis, carcinoma could not be excluded. A subtotal gastrectomy was then performed, the pathological report being benign gastric ulcer with chronic gastritis.

Comment: In this case, the radiologist was apparently always able to demonstrate a gastric ulcer except when healing had taken place. The gastroscopist, however, was twice unable to visualize the ulcer although one was definitely found at operation only a week after the last gastroscopy. The radiologist noted on several occasions that the stomach was of an unusual shape which at one time he described as "retort shaped", at another time an "hour glass deformity". He frequently noted also that there was an unusual cascade formation of the stomach. The ulcer was described by x-ray as being high on the lesser curvature which is a relatively blind area for the gastroscope. The x-ray superiority in this case is another example of mechanical failure of the usual type of flexible gastroscope.

M. R. X-ray examination was performed three times during a period of one month. On the first examination there was a shadow in the prepyloric area which possibly represented a crater, on the second examination on the greater curvature side of the stomach about 3 cm. from the pylorus, there was a 5 mm. ulcer crater. About 1 or 2 cm. proximal to the pylorus another ulcer crater was demonstrated. Since the patient had two definite ulcers in the prepyloric region, although both of them appeared grossly benign, the radiologist suggested the possibility of malignancy because of the location. The third x-ray examination showed very little change. Ten days after the last x-ray examination, gastroscopy was performed, but the ulcers described by x-ray were not visible in spite of the fact that the gastroscopist described a normal peristaltic wave seen passing over a slightly reddened antrum to a tight closure at what appeared to be normal pylorus. The lesser curvature of the antrum, however, was not visible. The pylorus was seen only momentarily and could not be adequately studied. There was a superficial gastritis of the antrum. A subtotal gastrectomy was performed, the pathological report being multiple ulcerations and erosions, acute and chronic gastritis.

Comment: In this case of multiple benign prepyloric ulcers, x-ray examination was definitely superior to gastroscopy due to mechanical failure of the gastroscope to satisfactorily view the prepyloric area. That area is difficult to see and sometimes the examiner believes he sees it when he is actually seeing a prepyloric contraction or spasm.

Two Cases Illustrating the Limitations of X-ray in Benign Gastric Ulcer

H. W. X-ray examination was performed on three occasions on the first of which there was a questionable area just behind the angulus measuring 8 mm. in diameter at its base which was thought might represent an ulcer. On the second examination, two weeks later, no ulcer crater could be demonstrated. The third examination was done three months later revealing a definite small projection close to the angle of the stomach which was very suggestive of a small ulcer. The prepyloric area was definitely rigid, and there was a suggestion of a shelf formation. Although it was

possible to explain the findings on the basis of a benign gastric ulceration with secondary changes, the radiologist believed that the possibility of a carcinoma arising from the prepyloric area and extending upwards along the lesser curvature side was a definite possibility which he was unable to rule out. About two weeks after the last x-ray examination, gastroscopy was performed. With the indicator in the twelve o'clock position a constant ulceration on the lesser curvature aspect of the angulus was demonstrated. The lesion appeared to be about 1 to 1.5 cm. in diameter of slightly irregular shape, 2 or 3 mm. deep with a clean gray base and considerable reddening around the margin. Peristalsis was not distorted as it passed normally over the lesion. No nodular appearance was visible but the mucosa of the antrum and body in this region was red and edematous. The findings were those of a rather acute benign appearing gastric ulcer on the lesser curvature at the angulus. A few days later, subtotal gastric resection was performed, the pathological report being benign gastric ulcer with chronic gastritis.

Comment: This is one of the very few benign ulcer cases where gastroscopy was more accurate than x-ray.

B. W. X-ray examination was reported as showing a leather bottle type of stomach which "without a doubt represents a scirrhus carcinoma." This appeared to involve at least the lower two-thirds of the stomach and the smoothness of the fundus made it possible that the entire stomach was involved. The films were compared with those taken elsewhere nine months ago and showed no definite change in the appearance of the stomach. Gastroscopy, however, failed to show any evidence of carcinoma. The angulus appeared normal. Peristalsis was absent. The proximal part of the antrum was not visible. In the body of the stomach, the mucosa showed a granular increased reddening and in some areas blood vessels were visible particularly along the anterior wall. No erosion, ulceration or neoplasm was demonstrable. The findings were those of superficial gastritis with some areas of gastric atrophy. About a week later, a transthoracic partial gastrectomy was performed, the pathological examination showing two active benign gastric ulcers with chronic gastritis.

Comment: The two ulcers as described by the surgeon were both small and superficial lying on the posterior wall just distal to the angulus. It is not surprising that these were missed by gastroscopy as this area is difficult to bring into view. The surprising fact about this case is that two different radiologists at an interval of nine months, were both so positive that they were dealing with carcinoma. Although the gastroscopist failed to see the two superficial ulcers, he did describe gastritis and did not make the error of describing the lesion as a very extensive carcinoma.

Summarizing the cases of pathologically proven benign gastric ulcer, there were eight cases in which both x-ray and gastroscopy arrived at the correct diagnosis, five cases in which both methods failed to give a correct diagnosis, six cases in which gastroscopy was limited (five times by mechanical failure), and only two cases where x-ray was more limited than gastroscopy.

JEJUNAL ULCER

In this group there were only two cases, in both of which gastroscopy was more limited than x-ray, once because of mechanical failure, and once because the marginal ulcer shown at x-ray and proven at operation looked like carcinoma by gastroscopy.

Two Cases Illustrating the Limitations of Gastroscopy in Jejunal Ulcer

P. C. This patient had six x-ray examinations of his stomach during a period of eleven months. In the first examination, the findings were not definitely conclusive. They indicated a posterior gastroenterostomy without evidence of marginal, gastric or jejunal ulcer. They were suggestive of a tumor in the region of the lower esophagus and cardia. The second examination, four days later, showed a mass involving the lower inch of the esophagus as well as the fundus of the stomach. The third examination, one week later, showed no proved neoplasm. The changes were possibly due to very marked gastritis. Two days later, gastroscopy was performed revealing only a moderate degree of superficial gastritis involving the antrum and body of the stomach as well as the stoma. One month after gastroscopy, the patient was re-examined by x-ray at which time the radiologist was fairly certain that this patient did not have malignancy but instead a severe gastritis. Nine months elapsed before a fifth gastrointestinal series was done at which time there was a constant 1 cm. fleck at the gastroenterostomy stoma which was diagnosed as a stomal ulcer. Six days later the gastroscopist was unable to bring the stoma into view because of spasm of the body of the stomach. There was considerable reddening of the crests of the rugae, some adherent secretion and edema, as well as marked verrucous changes especially along the lesser curvature and in the valleys between the folds. The findings were those of superficial and hypertrophic gastritis. Three weeks later, the patient was operated upon and a jejunal ulcer resected. The pathological report was jejunal ulcer, chronic gastritis, chronic jejunitis.

Comment: X-ray examination revealed a definite stomal ulcer which was invisible to the gastroscopist for mechanical reasons, namely, marked spasm of the body of the stomach preventing any view of the stoma.

C. L. X-ray examination was done twice. The site of the anastomosis was rigid. The mucosa of both the adjacent stomach and jejunum is edematous. The lesser curvature side of the anastomosis showed a very suggestive ulceration possibly involving a considerable area in the region of the anastomosis. The findings were those of marginal ulceration of the gastrojejunal anastomosis. Two days later, gastroscopy was performed and was described as follows: With the indicator in the seven o'clock position there was a lesion apparently about 10 or 12 cm. in diameter with a 1 cm. deep ulceration in the center of it. The ulcer was about 1.5 cm. in diameter with sharp margins surrounded by a very red, indurated appearance where normal rugae were absent. Surrounding this induration there was a nodular, elevated margin. The whole appearance was consistent with a rather large, ulcerating carcinoma occupying a large portion of the greater curvature and anterior wall in the

mid portion of the body of the stomach. Its relationship to the stoma was not accurately determined but it appeared to be proximal to it. A second x-ray examination was performed five days after the gastroscopy. At that time a large crater measuring approximately 1.5 cm. in diameter and 1.5 cm. in depth was seen on the anterior wall of the stomach just above the anastomosis. It was surrounded by an area of marked infiltration, the area of induration measuring approximately 7.5 cm. in diameter. There was convergence of the folds toward the crater. Grossly, the appearance was that of benign ulcer, but considering the history of recurrent gastric ulcer following resection, the radiologist believed that histological malignancy was a definite possibility. The anastomosis was included in the area of induration, and there was possibly another shallow ulcer present at the edge of the anastomosis. Operation was performed six days later and resection of the lesion accomplished. The pathological report was two anastomotic ulcers, one 2 cm. in diameter, and one 1 cm. in diameter.

Comment: In spite of a fairly satisfactory view of this lesion, the gastroscopist was wrong in believing this was a carcinoma. The radiologist although grossly describing the appearance as that of a benign ulcer believed that histological malignancy was a definite possibility. Both examiners were apparently somewhat confused by the very large amount of induration.

GASTRITIS

Five cases fall into this group. These patients were operated upon because they were thought to have ulcer or carcinoma or because of severe hemorrhage. In one case, the radiologist and gastroscopist were both correct in the diagnosis of gastritis. In one case, both were incorrect, in that both methods failed to demonstrate any lesion whatsoever. In one case gastroscopy was more limited than x-ray, and in two cases x-ray examination was more limited than gastroscopy.

One Case Illustrating the Limitation of Both X-ray and Gastroscopy in Proven Gastritis

J. F. This patient came in because of massive bleeding and neither x-ray nor gastroscopy could find the cause for it. Two x-ray examinations were done at intervals of two and a half months, both of which were entirely negative. Gastroscopy was done about ten days after the second x-ray and although a good view was obtained, no lesion was demonstrable. On the basis of massive hemorrhage, the patient was operated upon and a subtotal gastrectomy performed. The pathological report was hypertrophic gastritis with erosions. The serosa was smooth and glistening. The wall was thin and pliable. In the mid portion of the anterior wall 2 cm. from the distal resection edge there was an indefinite ulcer crater measuring 5 mm. in diameter. Just above this there were two shallow depressions with a faint pink base measuring 9 mm. in diameter. The remainder of the mucosa was pale and glistening.

Comment: In this patient, x-ray and gastroscopy both failed completely to show any lesion whatsoever in the stomach. Massive hemorrhage, however, made it imperative to operate upon this patient, and a definite gastritis with erosions was demonstrated pathologically. This is an unusual example of the limitation of both methods.

One Case Illustrating the Limitation of Gastroscopy in Proven Gastritis

W. M. J. Six years prior to resection, the radiologist demonstrated an old duodenal ulcer with no evidence of a gastroenterostomy stoma (in spite of a history of posterior gastroenterostomy). Gastroscopy was also done at this time showing superficial gastric ulcer with hypertrophic gastritis. The stoma was not seen by gastroscopy. Six years later, x-ray examination demonstrated an active duodenal ulcer with thickened gastric folds and excess gastric secretion. Gastroscopy one week later indicated an essentially normal appearing stomach except for a partially closed gastroenterostomy stoma. A subtotal gastrectomy was performed, the pathological report being chronic gastritis.

Comment: In this case, x-ray not only demonstrated an active duodenal ulcer but revealed thickened folds and increased secretions in the stomach suggesting gastritis. The gastroscopist was unable to see any gastritis. The pathologist, however, reported chronic gastritis, an almost routine pathological finding in association with an active duodenal ulcer. It is generally conceded that gastroscopy is superior to x-ray in the diagnosis of gastritis, but here is a case which does not bear that out.

Two Cases Illustrating the Limitation of X-ray in Proven Gastritis

D. B. X-ray examination of the upper gastrointestinal tract showed the esophagus and fundus of the stomach to be normal. At about the angle of the stomach, the lesser curvature side appeared rigid with a constant filling defect which involved the prepyloric area down to the greater curvature (fig. 7). There was one ulceration close to the prepylorus, and smaller ulcerations at the lesser curvature side near the antrum. The findings were those of carcinoma of the antrum and prepyloric area of the stomach. Eight days later, a gastroscopy (fig. 8) was performed and reported as follows: The angulus appeared slightly reddened and a little verrucous. Normal active peristalsis was seen passing over a somewhat reddened antrum to a tight closure at what appeared to be normal pylorus but it may have been prepyloric spasm. No ulcerations or erosions were visible in the antrum. Proximal to the angulus there were several small 1-4 mm. depressions some of which contained mucus consistent in appearance with erosions or superficial ulcerations. In this area there was a somewhat verrucous appearance. The body of the stomach was reddened with some edema and adherent secretion. No rigidity was demonstrable. No tumor was visible. The findings were consistent with superficial and hypertrophic gastritis with erosions and ulcerations. No neoplasm was visible but the gastroscopist was not willing to exclude the possibility of a neoplasm beyond the reach of the gastroscope. The following day a partial gastrectomy was performed, the pathological report being chronic gastritis.

Comment: Gastroscoy gave the correct diagnosis in this case whereas the x-ray examination was incorrect in reporting a carcinoma which was not found at operation. In such cases, the difficulty is to know whether to believe the radiologist or the gastroscopist, and the surgeon must always err on the side of exploring a patient and finding no carcinoma, rather than not exploring him and leaving a carcinoma to grow until it may become hopelessly inoperable.



FIG. 7. D. B. X-RAY SHOWING A RIGID LESSER CURVATURE WITH A CONSTANT FILLING DEFECT IN THE PREPYLORIC AREA CONSIDERED BY THE RADIOLOGIST TO BE CARCINOMA

The gastroscopist, however, reported superficial and hypertrophic gastritis with erosions and ulcerations. The pathological report was chronic gastritis. See fig. 8.

G. G. S. This patient had had several episodes of severe gastrointestinal bleeding. X-ray examination one and a half years before resection failed to show any cause for the bleeding. Severe hemorrhage recurred a year and a half later at which time re-examination of the upper gastrointestinal tract revealed no definite evidence of disease. Gastroscoy was performed the following day and on the lesser curvature just proximal to the angulus there was increased reddening and higher up on the lesser curvature there was a slightly verrucous appearance. There was no edema, adherent secretion, erosion, nor active bleeding. There was no blood in the stomach.

The findings indicated a minimal amount of superficial and hypertrophic gastritis. Gastric resection was performed a month later, the pathological report being severe chronic gastritis with multiple erosions. Three shallow ulcers the largest measuring 5 mm. in diameter were found encircling the pyloric ring. The base of each ulcer was hemorrhagic containing crusted blood. The edges were punched out. The surrounding duodenal and gastric mucosa was injected and finely granular for a radius of 3 cm.

Comment: The radiologist here was unable to find any definite evidence of disease in the stomach. There was no appreciable thickening of the gastric mucosa. The gastroscopist, however, reported slight superficial and hypertrophic gastritis. A much more severe gastritis was found pathologically than was reported gastroscopically. The gastroscopist reported a normal rather active peristaltic wave passing over a normal appearing antrum to a tight closure at what appeared to be normal pylorus. Quite possibly, the contraction seen by the gastroscopist was a prepyloric contraction due to spasm and the most severe gastritis near the pylorus was not visible.

BENIGN TUMOR

There are two cases in this group in one of which x-ray and gastroscopy were correct and in the other of which gastroscopy made the diagnosis of multiple polyps which were not visible by x-ray.

X-ray and Gastroscopy Both Essentially Correct (1 Case)

T. H. Two x-ray examinations were performed the first of which demonstrated a slightly localized filling defect in the antrum of the stomach measuring about 2 cm. in diameter produced by something very soft which could not be moved from this region. Re-examination was requested to rule out food as the cause of the polypoid defect described. Repeat examination confirmed the presence of localized thickening of the wall of the stomach in a circumscribed area of the antrum. The stomach appeared quite flexible in this region. The shape of the swelling was not quite as constant as usually seen in polyp. The findings were those of definite abnormality in the antrum of the stomach. The appearance was consistent with a sessile polyp or tumor of the stomach but a few features were unusual, as it was more difficult to demonstrate than a polyp and shaped not quite as constant as seen in polyp. Gastroscopy was performed two days later (fig. 9). Beginning at the angulus of the stomach with the indicator in the one o'clock position, there was visible in the seven o'clock position of the field a smooth, rounded, submucosal mass approximately 2-3 cm. in width and probably 6-8 cm. in length, extending toward the pylorus and apparently lying on the anterior wall toward the greater curvature. It appeared to be in two lobules which were connected. They appeared soft and peristalsis passed over them without any rigid deformity. No ulceration was visible. The mucosa overlying the tumor seemed to be of smooth consistency and normal color. The mucosal folds extended just proximal to the angulus up to the edge of the tumor mass and then seemed to smooth out over the mass just beyond the angulus. There seemed to be

little obstruction to the antrum but as the wave went down the tumor obstructed the lumen. This was only temporary, and should not produce symptoms. The mucosa throughout the rest of the body of the stomach appeared normal. The pylorus could not be seen beyond the tumor. The estimated depth of the tumor was about 1 cm. The findings were those of a tumor in the antrum of the stomach which the gastroscopist felt almost certain was benign, most likely a neurofibroma or fibromyoma. Six days later a 1.5 cm. encapsulated tumor mass was found present on the serosal surface of the antrum of the stomach near the greater curvature. A gastrotomy was done and the tumor mass excised locally. The pathological report was leiomyoma.

Comment: Both the radiologist and the gastroscopist were reasonably satisfied as to the benign nature of this tumor, the gastroscopist confirming the radiologist's impression and being more specific in his description and diagnosis.

One Case Illustrating the Limitation of X-ray in Proven Benign Tumor

B. D. This patient was admitted because of gastrointestinal hemorrhage. Six months before gastric resection, x-ray examination revealed what was thought to be a duodenal ulcer. The patient was explored, a duodenotomy performed, and no lesion found. Two weeks later a gastroscopy was done. With the indicator in the eleven o'clock position a 5 mm. rounded elevated mass was seen on the greater curvature aspect of the angulus on the crest of one of the folds. A similar lesion was seen toward the posterior wall on the angulus. These had the appearance of small benign polyps but could be pseudo-polyps or hypertrophied folds. There was an area of hemorrhage on the greater curvature bright red blood being present in the lumen of the stomach. The findings were consistent with two small polyps or pseudo-polyps with some blood in the stomach, origin undetermined. The hemorrhage continued after discharge from the hospital, and he was re-admitted approximately five months after the duodenotomy at which time he was re-examined by x-ray and the stomach found to be normal as to form and function. There was no evidence of polypi or other lesion. The duodenal bulb was constantly deformed and along the superior margin there was a persistent fleck of barium which looked like an ulcer but could have been due to scarring from the duodenotomy. Gastroscopy was repeated and at this time four or five polyps were visible (fig. 10). A subtotal resection was then performed, the pathological report was gastric polyps; superficial gastritis with erosion.

Comment: The gastroscopist was able to see several small polyps which were not visible by x-ray.

LYMPHOMA

One Case Illustrating the Limitation of X-ray and Gastroscopy in Proven Lymphoma

H. J. This thirty-seven year old man was admitted for gastroscopy because of severe repeated gastrointestinal hemorrhage. X-ray examination before admission had revealed a definite ulcer crater on the greater curvature in the prepyloric region. This had shown progressive healing and on subsequent x-ray study there had been

complete disappearance of the crater with, however, a remaining area of apparent induration proximal to the lesion. Gastrosocopy demonstrated a thickened angulus, on the greater curvature side of which there was a constant thick rugal fold about 8 mm. in diameter which extended from just proximal to the angulus and was seen in the antrum extending all the way to what appeared to be normal pylorus. Peristalsis was active and was constantly deformed by this fold and also presented a slightly eccentric appearance. In other words, the peristaltic ring as it passed from the angulus to the pylorus was not a true circle, nor did it present the usual thin edge. The edge of it was thickened and the circle was deformed, especially on the greater curvature. Moreover, the antrum appeared narrowed and tubular. It was not, however, completely rigid but was partly distensible with air. No ulceration was seen in the antrum. Proximal to the angulus on both curvatures, there were several hemorrhagic erosions, each one being about 5 or 6 mm. in diameter. There was some bright red blood in the body of the stomach. The mucosa showed some increased reddening, thickening, and edema. The findings indicated an abnormality of the antrum which was not definitely characteristic. There was definite superficial gastritis with erosions and hemorrhage. Benign tumor, leiomyosarcoma, lymphoma, and carcinoma were considered possibilities. X-ray examination was performed the following day. The fundus of the stomach appeared normal. From a point high on the lesser curvature about 2 cm. below the cardia, the lesser curvature was definitely abnormal. It was not as pliable as usual and peristaltic waves were small. The distal cm. in the prepyloric area was not remarkable but just proximal to this there was an area which did not appear to change and opposite this on the greater curvature, there was likewise some stiffness. In both of these areas, there appeared to be shallow areas of ulceration. The duodenal cap and loop were not remarkable. A definite radiological diagnosis was not made, but the following were considered: syphilis, benign ulcerations, and possibly a scirrhus type of carcinoma. One month later, x-ray examination was repeated and showed very little if any change in the stomach, esophagus, or duodenum. Gastrosocopy was also repeated (fig. 11). The angulus was in a good deal of spasm during most of the examination but relaxed enough to allow many vigorous peristaltic waves to pass down a narrow reddened antrum. Large reddened folds extended from the angulus into the antrum and on the crest of one of these folds there was an erosion about 4 mm. in diameter surrounded by some reddening and secretion but no active hemorrhage. The erosion appeared to be on the lesser curvature of the antrum. On the posterior wall of the antrum there was irregular reddening and a slightly elevated appearance. When the angulus contracted, it did not do so in a circular manner but was slightly distorted. On the posterior wall just proximal to the angulus the mucosa presented an irregular blotchy red and white appearance with some slightly nodular elevations and a suggestion of some irregularity. The gastroscopist felt no doubt the stomach was abnormal with definite superficial gastritis and erosions. "If the patient has a tumor, I am now inclined to put lymphoma first, carcinoma second, with other types of tumor much less likely." A subtotal gastrectomy was done the following day, the pathological report being malignant lymphoma, lymphocytic type. Regional lymph

nodes were negative. There was present a very severe gastritis making it difficult for the pathologist to determine exactly the extent of the lymphoma.

Comment: The diagnosis of lymphoma is extremely difficult either by X-ray or by gastroscopy. The writer recalls one case of proven lymphoma in which one radiologist suggested the possibility of lymphoma because of the enormously thick folds in the fundus of the stomach. Many subsequent radiologists did not raise the question of lymphoma. In that case, the gastroscopist noted a very marked cobblestone appearance with multiple superficial ulcerations. In the present case, there were many of the same signs as were noted in the other case, namely, extremely thick folds extending even into the antrum where such folds are not usually visible to the gastroscopist, marked cobblestone appearance, some distortion and rigidity with poor response to air inflation, erosions and superficial ulcerations which appeared and disappeared in different areas at different examinations. The gastroscopist, although obviously not certain, put lymphoma first among the tumor possibilities. With the above findings in mind, perhaps the diagnosis of lymphoma can be made or at least suspected more often.

NORMAL POSTERIOR GASTROENTEROSTOMY STOMA

One Case Illustrating the Limitation of X-ray in a Normal Posterior Gastroenterostomy Stoma

A. F. This sixty-two year old woman was sent into the hospital because of an outside x-ray diagnosis of carcinoma of the stomach. The first x-ray examination done in this hospital showed no evidence of disease in the esophagus, stomach, or duodenum. Three days later, however, a gastrointestinal series revealed a small filling defect in the antrum of the stomach measuring approximately 2 cm. in diameter. The defect was lobulated and was closer to the greater curvature. At times, there was a questionable crater appearing in the region of the lesion. The appearance was that of a localized small lesion in the antrum most likely a small sessile tumor or a congenital variation (aberrant pancreas or abnormal mucosal arrangement are less likely possibilities). Gastroscopy two days later was reported as follows: a normal peristaltic wave was seen passing over a normal appearing antrum to a tight closure at what appeared to be normal pylorus. On the posterior wall of the antrum unusually near the pylorus, there was a normal appearing gastro-enterostomy stoma. The stoma appeared to be of normal size and a good view was obtained well into the jejunum probably for a distance of at least 10 or 12 cm. No abnormality was noted. Re-examination by x-ray the following day showed the soft polypoid mass in the distal portion of the antrum to be produced by a posterior gastroenterostomy with slight projection of the anastomosis into the lumen. A small amount of barium passed through the anastomosis, most of the barium passed through the pylorus. No operation was performed, but the gastroscopist's findings were confirmed by the second x-ray.

Comment: This is a very unusual case where a normal posterior gastroenterostomy was well demonstrated by gastroscopy but was at first thought to be a possible antral tumor by x-ray.

NORMAL STOMACH

X-ray and Gastroscopy Both Correct (1 Case)

W. R. On the first x-ray examination a filling defect was seen in the region of the angle of the stomach which had more the appearance of foreign material than of tumor. Re-examination of the stomach four days later was again somewhat handicapped by fluid within the stomach but no intrinsic lesion was seen. The pylorus opened readily. The cap was not deformed. Only the uppermost portion of the medial wall of the second portion of the duodenum was somewhat smoother than usual. The findings were not definite enough to make a diagnosis of a mass in the region of the head of the pancreas. Gastroscopy was performed the following day, the stomach contained large amounts of secretion which interfered with the view of the body of the stomach. The angulus, however, was fairly well seen and appeared normal with normal peristaltic wave passing over a normal appearing antrum to what appeared to be tight closure at a normal pylorus. X-ray examination was performed on two subsequent occasions within about a month and each time showed pressure on the antrum as well as on the second portion of the duodenum suggesting a mass in the region of the head of the pancreas which prevented emptying of the stomach in the supine position but allowed fairly good emptying of the stomach with the patient in the right lateral position. The day after gastroscopy the patient was explored, cholecystectomy performed, and an area of cystic degeneration of the pancreas was found along the lesser curvature of the stomach near the prepyloric region as suggested by x-ray. The pathological report was cholecystitis and cholelithiasis.

Comment: Both the radiologist and the gastroscopist were correct in reporting a normal stomach. The radiologist was more helpful in suggesting a mass in the region of the head of the pancreas.

One Case Illustrating the Limitation of X-ray in a Proven Normal Stomach

F. H. This seventy-seven year old man was admitted for gastroscopy because of hematemesis, melena, and an outside x-ray examination which showed a filling defect in the fundus of the stomach. Because of the x-ray report, gastroscopy was done immediately after admission to the hospital. Except for some reddening and edema in the body of the stomach, gastroscopy was negative. The findings were consistent with a moderate degree of superficial gastritis. A neoplasm in the blind area of the fundus could not be positively excluded. X-ray examination was repeated and demonstrated an inconstant irregularity in the cardia. Three weeks later, the x-ray examination was repeated and revealed quite a change in the appearance of the stomach since the last examination. The fundus of the stomach presented "a quite constant contour in several films as though the wall were infiltrated, and one seeing this now for the first time would certainly be suspicious of neoplasm." About two weeks later, a transthoracic exploration of the esophagus and stomach was carried out. No neoplasm was demonstrable.

Comment: Two different radiologists were sufficiently definite about the presence

of a neoplasm in the fundus of the stomach that operation was advised. The gastroscopist was unable to visualize any lesion but could not exclude a possible neoplasm in the blind area of the fundus. Exploratory operation was negative.

DISCUSSION

In this series of 53 cases there were 19 proven carcinomas in 10 of which x-ray and gastroscopy were both correct, in one both were incorrect, and in 8 one method was more accurate than the other, 6 times in favor of gastroscopy, twice in favor of x-ray. In the previous series of 245 cases x-ray was superior in 32 cases, gastroscopy superior in only 20. This shift in favor of gastroscopy may mean that with greater experience and with improvements in the mechanics of the instrument the gastroscopist is getting a larger percentage of correct diagnoses in carcinoma. Whereas in the previous series there were 32 gastroscopic failures, 25 of which were listed as mechanical, in the present series there was only one mechanical failure of the gastroscope in carcinoma. Comparisons are not quite fair as the present series is much smaller. Definite improvements in the instrument include the ability to change the angle of the mirror in two of the American gastroscopes, and proximal control of the flexible part in one of the English instruments.¹ Thus lesions are better seen and more accurate diagnoses are obtained.

In the ulcer group, however, there has been no appreciable improvement in gastroscopic diagnosis, all except one of the 6 failures in the present series being mechanical. The improvements in the gastroscope mentioned above have not benefitted the ulcer group so much as the cancer group because (1) ulcers are often smaller and harder to see than carcinomata; (2) the mechanical improvements referred to have not helped very much in visualizing the lesser curvature of the antrum and prepyloric area where many small ulcers occur; and (3) the English gastroscope which helps so much with lesions high on the lesser curvature and posterior wall has only very recently been used to any extent by the writer.

There were only 2 jejunal ulcer cases in this series and as in the previous series of 8 jejunal ulcers the limitations of gastroscopy are again demonstrated. The gastroscopist made an erroneous diagnosis of carcinoma in one and encountered too much spasm in the other to permit any view of the lesion. The radiologist was correct in both instances.

In the diagnosis of gastritis gastroscopy has generally been considered the best method of diagnosis, but in 2 out of 5 pathologically proven cases in this series

¹ I refer to the Herman Taylor flexible gastroscope which I found at first unsatisfactory due to porous wartime rubber and consequent fogging of the lenses. This has now been repaired and I am finding it excellent.

gastroscopy failed to reveal any gastritis. In one of these x-ray examination was also negative but in the other the radiologist reported thickened folds and increased secretions. In the remaining two cases of gastritis the radiologist in one reported carcinoma and in the other failed to find any definite evidence of disease. Although gastroscopy may occasionally fail to demonstrate gastritis which is later proven by the pathologist it is still the only method which has been reasonably well correlated with the pathological findings (2, 3).

No generalizations can be made from the 6 remaining cases scattered in 4 groups. In one of the 2 cases of benign tumor the gastroscopist was able to visualize multiple small polyps not visible by x-ray. In the other benign tumor case the gastroscopist was more specific in his description and diagnosis than the radiologist, but considerably overestimated the size of the leiomyoma. In the only lymphoma case in this series the gastroscopist diagnosed severe superficial gastritis with erosions and was strongly suspicious of lymphoma. Not long after this, however, he was incorrect in putting lymphoma as first choice in a case of benign ulcer (see E. G.). A fourth case in this miscellaneous group was an unusual one illustrating the limitation of the radiologist in visualizing a normal posterior gastroenterostomy stoma. In one of 2 proven normal stomachs x-ray and gastroscopy were both correct, the radiologist being more helpful in diagnosing extrinsic pressure from a mass in the region of the head of the pancreas. In the other normal stomach two radiologists were so suspicious of carcinoma in the fundus of the stomach, that exploratory operation had to be performed. No tumor was found and none had been seen by the gastroscopist but he had not been able to positively exclude the possibility of carcinoma in a blind area of the fundus.

Summarizing the results of x-ray and gastroscopy in the above 53 cases both methods reached the correct diagnosis in 21, both were incorrect in 8, x-ray was more accurate than gastroscopy in 11 but gastroscopy was more accurate than x-ray in 13. If the 8 cases in which gastroscopy was limited because of mechanical difficulties are excluded, there remain only 3 cases in which x-ray was more accurate than gastroscopy. In other words if the gastroscopist can get an adequate view of the lesion his chances of making a correct diagnosis are greater than those of the radiologist.

CONCLUSIONS

The limitations of radiology and gastroscopy have been pointed out in 53 cases of proven carcinoma, gastric ulcer, jejunal ulcer, gastritis, benign tumor, lymphoma, normal posterior gastroenterostomy stoma, and normal stomach.

In demonstrating the limitations of both methods of examining the stomach the value of each as it supplements the other is clearly brought out. The two

methods are not competitive but supplementary, and greater diagnostic accuracy is attained when both are used cooperatively than when either is used alone.

The mechanical limitations of gastroscopy still present various difficulties but efforts to correct them have already met with some success.

If the gastroscopist can get a satisfactory view of the lesion his chances of arriving at a correct diagnosis appear to be greater than those of the radiologist.

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THE VALUE OF GASTROSCOPY TO THE CLINICIAN*

CHESTER M. JONES, M.D.

*Physician, Massachusetts General Hospital, Boston, Clinical Professor of Medicine,
Harvard University*

It is now thirteen years since examination of the stomach by means of a flexible gastroscope was first performed in this country by Benedict. Previous to that time the limitations imposed by the rigid open-end gastroscope had precluded its use as an instrument of real diagnostic value. The flexible scope, devised by Schindler and Wolff; is free from most of the dangers inherent in the previous instruments and it has made possible direct inspection of most of the gastric surface.

Schindler's original observations, plus those that have accumulated in recent years, constitute an important contribution to our knowledge of gastric change under disease, and, to some extent, under physiological conditions. It is pertinent, I think, that I be permitted to evaluate the results that have accrued from the use of gastroscopy, from the point of view of the interested bystander. I believe I can qualify on both counts of interest and standing-by. As far as Dr. Benedict is concerned, I have been, while looking over his shoulder, both enthusiastic and critical. It has long been my opinion that new procedures, in order to obtain the optimum lasting value as accessory diagnostic measures, need the constant application of both enthusiasm and scepticism on the part of the clinician.

To the question, "Is gastroscopy of real clinical value?" the answer should be a definite affirmative. There can be no doubt that it has contributed important and decisive information, both as a diagnostic procedure supplemental to careful roentgenologic studies, and as a unique, direct source of information. That such is the case does not diminish the fact, to my mind, that it also has definite limitations and that not infrequently it contributes some uncertainties. This seeming contradiction, however, places it in a position no different from that of all diagnostic measures.

Gastroscopy alone permits one to make an accurate diagnosis of gastritis. No other measure can provide the definite information necessary to this diagnosis. Whether one can state as readily that the term gastritis is used by all gastroscoipists with equal accuracy and understanding is quite another matter. Granting for the moment that the diagnosis of gastritis is accurately and conscientiously employed, there is little doubt that the demonstration of this condition has been an outstanding contribution to the elucidation of many

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cases of previously unexplained hemorrhage. The value of this particular contribution must be stressed. In the absence of demonstrable roentgenologic abnormalities, major bleeding episodes frequently have been adequately explained by gastroscopic findings. Although, unfortunately, there are still cases of mysterious upper gastrointestinal bleeding, the number is constantly being reduced by integrated radiologic, gastroscopic and esophagoscopy studies. I have included esophagoscopy because, in a sense, it embodies gastroscopic observation in one particular group of cases, namely, that of the patients bleeding from moderate-sized paraesophageal hernias. Here the long esophagoscope can at times demonstrate the congested bleeding area in the herniated portion of the stomach, while the remainder of the stomach, visualized by routine gastroscopy, may be entirely normal.

There are other values to be placed on the work done by an experienced gastroscopist. He always supplements roentgenologic studies of the stomach, and I believe that the demonstration of a gastric lesion by the radiologist should usually imply confirmation by the gastroscopist. As all of you know, there is a small group of cases in which the endoscopist has visualized lesions not shown by x-ray. The reverse is, of course, equally true. Of greater import, however, is the agreement, or lack of agreement, present between the radiologist and the gastroscopist in the presence of a known gastric lesion. I refer to the differentiation between benign and malignant lesions. To my mind, it is futile to engage in a controversy over the accuracy or infallibility of either procedure in solving this most important problem. In the final analysis, neither method can be entirely accurate or infallible. In doubtful cases, of which there are many, it is impossible for either to provide more than moderate assurance of the probable diagnosis; the final decision must depend on a correlation of all known facts, including progress of the lesion, the frequent demonstration of a histamin-achlorhydria, and the like.

That one must continue to entertain doubts is obvious when one remembers the occasional case in which complete healing of gastric ulceration seemed assured by repeated roentgenologic examinations, and gastroscopic studies indicated restoration of normal mucosal continuity, but in which the patient returned subsequently with obvious and perhaps inoperable cancer. By this I do not mean that all gastric ulcers, or even the majority of them, require resection. I do wish to infer that the limitations of any diagnostic procedure must be recognized, and not overlooked to the point of anything approaching complacency.

In the presence of gastric ulcerations, the best practice is to employ gastroscopy plus radiologic observation on repeated occasions until one can be assured that the risk of unrecognized cancer has been eliminated. I believe that no gastroscopist would be right in stating that he can always differentiate between

benign and malignant processes, but in doubtful cases I still want his help in trying to make such a differentiation.

In addition to the foregoing, gastroscopic visualization of other gastric lesions, such as adenomatous polyps, leiomyosarcomata, lymphomata, and the like, is of extreme value in directing proper therapeutic measures.

Whether or not the obtaining of biopsy material by gastroscopic means is of real value is open to question. In any obviously malignant process it is preferable to accomplish this by surgical removal. In doubtful cases, the chances of obtaining adequate material for microscopic study is remote. Certainly a negative biopsy finding in a doubtful case could not be accepted as final because of the frequent association of a benign inflammatory process with malignancy.

I am sure that the demonstration of gastritis by gastroscopy does not necessarily mean that the cause of bleeding has been found. On the contrary, a bleeding duodenal ulcer may not infrequently be associated with an easily demonstrable gastritis, which is quite innocent as far as blood loss is concerned.

Reverting to the diagnosis of gastritis, I have some reservations. The term *atrophic gastritis* should be limited to those cases in which there is no associated deficiency disease and possibly no general constitutional degenerative disease. More frequently than not, gastric atrophy under these conditions is not attributable to an inflammatory process but is simply a reflection of degenerative changes taking place throughout the organism. Adequate replacement therapy often modifies or restores to normal an atrophic mucosa incidental to such a process. The condition should be called gastric atrophy and so considered.

Gross hypertrophic changes, ulcerations or erosions are obviously associated with a true gastritis and should be so classified. The confirmation of gastroscopic diagnosis by histologic study of resected specimens by numerous investigators can leave no reasonable doubt as to the accuracy of gastroscopic observation when carried out by an experienced operator.

The most controversial point, to my mind, is the ease with which a diagnosis of superficial gastritis is made by certain observers in an attempt to explain symptoms. It is obvious, in many instances, that the visualization of a hyperemic, edematous, or hypersecreting gastric mucosa has been used as a substitute for sound clinical judgment in the evaluation of a patient and his symptoms. In discussing this particular issue, I should like to refer back to our first American gastroscopist, Beaumont. The gross changes that he noted in the stomach of Alexis St. Martin hold the key to much of the controversial matter that troubles clinicians and gastroscopists alike in relation to minor degrees of gastric alteration and symptomatology. In the case of Alexis, the effects of drink, anger, overeating, and other variables were reflected

in day-to-day changes in color, secretion and turgidity that corresponded closely to the gastroscopic changes now frequently labelled gastritis. The more or less transient hyperemia, pallor, excessive secretion, and the appearance of "aphthous patches" that were noted were striking modifications from normal but, in all probability, did not indicate a true gastric inflammatory process.

A century later Wolf and Wolff produced similar changes at will as a result of emotional stimulation; they recorded them by color photography, and watched them revert to normal. If such striking alterations can be demonstrated in the living human being, it must signify that the line between important functional changes of a transitory nature and the more permanent changes due to chronic inflammatory disease is a difficult one to draw with any degree of accuracy. It is even more difficult to be certain that readily visible alterations in the appearance of the gastric mucosa are the cause of symptoms. In many instances these alterations represent merely the reaction of the end-organ to overstimulation from distant centers. They are comparable to the striking motor, secretory and vascular changes that can be noted on sigmoidoscopic examination in patients with so-called mucous colitis or "irritable colon". Whether such changes are due to psychological disturbances or to local irritants is of little immediate consequence. The important fact is that hyperemia, turgidity, hypersecretion, or the reverse, may be due to irritation from a variety of causes, many of which originate at a distance from the organ affected. These causes are frequently the focal point of difficulty, and are the source of symptoms rather than any local gastritis or colitis. This situation is comparable to the severe conjunctival irritation with intense lacrimation, hyperemia, and edema which is so commonly seen in a person who has suffered a serious bereavement and has wept copiously. The appearance of the eye may well simulate a conjunctivitis, yet actually it represents only a transient, external expression of grief.

The frequency with which definite changes can be demonstrated in the motor, secretory, and vascular functions of the stomach without any symptoms indicates clearly that conscientious thinking is needed in the interpretation and classification of the milder superficial gastric changes. The discrepancy between symptoms and gastroscopic findings was clearly demonstrated by Chamberlain in his recent paper. His attempt to differentiate sharply between psychoneurotic individuals and patients with gastritis on the basis of relatively minor gastric changes is open to some question. Halsted, in the *Mediterranean Theater*, observed similar gastroscopic changes in a certain proportion of 200 cases of "nervous dyspepsia", but was definitely in doubt as to which was cause and which effect, as far as symptoms were concerned. Thompson of Philadelphia examined 500 patients at St. Albans during the war. A certain

proportion of the group were sent from the Neuropsychiatric wards because of vague digestive symptoms. In these patients the digestive symptoms were not predominantly gastric but were part of a definite pattern of neurotic complaints. A significant number showed marked hyperemia, edema, and excessive mucoid secretion in the stomach, but those with the most apparent changes did not have any greater tendency to real gastric complaints than those with lesser changes. Of the remainder of the group, not coming from the psychiatric wards, less than half of the patients having gastric symptoms (anorexia, nausea, vomiting, and discomfort) showed objective evidence of so-called gastritis, and roentgen examinations were negative. Furthermore, intensive therapy with insistence on regulated dietary management, avoidance of tobacco, alcohol and coffee, and even gastric lavage with medicated solutions such as have been advocated by some in the treatment of gastritis, had little effect on either the symptoms or the gastric mucosal alterations when present. Both Thompson and Halsted are in doubt as to the wisdom of calling such gastric changes gastritis.

Obviously a final decision is still not forthcoming. I am sure, however, that gastroscopists and clinicians alike will contribute much more by withholding a definite classification of gastritis from this large group of patients who present minor mucosal changes in vascularity, motor and secretory activity *than by complacently applying the label of an inflammatory disease of the stomach and treating it rather than the individual and his habits.*

I have tried to point out the real contributions as well as some of the uncertainties attendant upon the use of gastroscopy. I might add one more contribution that it is gradually making, that of repeated observation of the appearance and behavior of the stomach in intercurrent disease, such as the deficiency states and specific infections. To know what the stomach is like in sprue and in infectious hepatitis is an important addition to our understanding of symptomatology in two important disease conditions.

DISCUSSION

DR. JOHN T. HOWARD: I suppose you know what I am going to say before I start, because it is always the same thing, but I am very glad that Dr. Jones minimized the importance of superficial gastritis and that in the differential diagnoses that were discussed today superficial gastritis was not mentioned.

For a long time, we have been reporting this as a red stomach rather than as a diseased stomach.

We are apt to make mistakes if we rely too much on gastroscopy alone.

I am glad to see here, and to gain the impression that the men who read papers today are having their patients operated on if the gastroscopic findings and the X-ray findings don't agree. There is a tendency to rely more on the X-ray than on the gastroscopic findings when they do not fit. I think this right, and that the diagnosis

of gastritis should be made only when the findings are definite. I am always afraid of missing a malignancy. Dr. Jones said the same thing.

Now, these operations are so simple and the mortality is so low that when gastroscopic examinations are equivocal, Dr. Pollard to the contrary notwithstanding, I think we had better have a peek in. I think Dr. Hodes said that same thing.

Yesterday we saw some pictures of cases that were suspected to be extensive carcinoma. I refer to Dr. Palmer's cases and to one case shown by Dr. Maurice Feldman. It occurred to me that some people in the audience might have felt in Dr. Palmer's cases that if the thing is carcinoma and it is so extensive, what can one do about it? As you know, complete gastrectomy can now be done. Dr. Palmer said this afternoon he did not advocate complete gastrectomy for hypertrophic gastritis. What can be done about it?

Well, if it is carcinoma we can't cure the patient, but with this complete gastrectomy technique the lives of enough patients can be prolonged, and if it is carcinoma the patient has nothing to lose. The success of the operation is rather high in Baltimore, and the lengthening of life is worth while, so that I rather agree that in cases of doubt, even when things look pretty pessimistic, there had better be an operation.

THE GASTROSCOPIC DIFFERENTIATION OF GASTRITIS FROM CARCINOMA OF THE STOMACH*

HERMAN J. MOERSCH, M.D.

Division of Medicine, Mayo Clinic, Rochester, Minnesota

A review of the literature dealing with gastroscopy in the differential diagnosis between gastritis and carcinoma of the stomach might readily lead one to the conclusion that gastroscopy enables one to make such a differentiation with the greatest of ease. This assumption is based in part on the fact that gastroscopy is supposed to be practically infallible in the diagnosis of gastritis. Doubt as to the accuracy of such a conclusion soon presents itself when one studies reports dealing with gastroscopy in the diagnosis of carcinoma of the stomach. Schindler and Gold (1), Konjetzny (2) and others have pointed out that during gastroscopy gastritis may at times be confused with carcinoma. Schindler (3), in 1939, ably reported seven cases of gastritis which presented a gastroscopic picture that could not be distinguished from that of carcinoma of the stomach, and in which the diagnosis was established only on microscopic examination.

Although there exist many references in the literature to the possible role of gastritis as a predisposing factor in the development of carcinoma of the stomach, there has been a sparsity of reports as to the accuracy of gastroscopy in distinguishing between the two conditions. This scarcity of information is due largely to the fact that abdominal exploration is seldom performed on patients because of gastritis and therefore microscopic confirmation of the diagnosis is lacking. The microscopic diagnosis of gastritis is likewise not without pitfalls, as Crohn (4) has so well pointed out, for most stomachs, especially those of adults, will show some evidence of inflammatory change, a normal gastric mucosa being indeed very rare. To add to the difficulty, there exists a difference of opinion among gastroscopists as well as pathologists as to what actually should be classified as gastritis and what constitutes a normal physiologic change. In this paper, only those cases in which the changes are obvious and meet the criteria generally accepted as those of gastritis are classified, after gastroscopic examination, as gastritis.

In any attempt to evaluate the accuracy of gastroscopy in the differential diagnosis between gastritis and carcinoma of the stomach one must take cognizance of the fact that the two conditions frequently coexist in the same stomach. Although a gastroscopic diagnosis of gastritis may be correct in a

*Read at the annual meeting of the American Gastroscopic Club, Atlantic City, New Jersey, May 26, 1946.

case of this type, if the coexisting carcinoma was overlooked the gastroscopic diagnosis, in the present study, will be regarded as incorrect.

CLINICAL STUDY

Yesterday, before the American Gastro-Enterological Association, in discussing the value of gastroscopy in the diagnosis of carcinoma of the stomach, Dr. Kirklin and I (5) reviewed 100 selected cases of proved carcinoma of the stomach in which gastroscopy had been performed, and pointed out that gastritis is the condition most frequently confused with carcinoma. In this group of cases, the carcinoma had been misinterpreted as gastritis on gastroscopic examination in eleven instances. Although the group was a selected one, all cases being chosen to illustrate the more difficult diagnostic problems, still this result emphasizes how frequently carcinoma may simulate gastritis, and shows the great care that must be exercised to distinguish between the two. It would seem appropriate, in order to obtain a more accurate understanding of the diagnostic difficulty involved in the differential gastroscopic diagnosis between gastritis and carcinoma of the stomach, to review 100 cases of microscopically proved gastritis and see if the same error in diagnosis existed in this group as in the cases of proved carcinoma.

In this group of 100 cases, a gastric operation had been performed and the diagnosis of gastritis had been confirmed by gross inspection of the interior of the stomach and also by microscopic examination of tissue. The patients had all undergone both gastroscopy and roentgenologic examination of the stomach preceding the gastric operation. In passing, it might be well to mention that gastric operation had been performed in the majority of the cases for other clinical reasons than that a gastroscopic diagnosis had been made of gastritis.

There were seventy-eight men and twenty-two women in the group. The youngest patient was twelve years of age and the oldest, seventy-five, the average age being forty-seven years. Thirty-nine of the patients had undergone previous operation on the stomach, while the remainder had been free of such an experience. All of the patients gave a history of gastric distress. In eighty of the 100 cases, as shown in table 1, gastroscopic examination preceding operation had been reported as revealing gastritis. In twenty cases, the gastroscopic diagnosis had been erroneous. It is of interest to note that the percentage of error was much lower for those patients who had undergone previous operation on the stomach than for those who had not. This is not surprising, as Walters and I (6) had previously found that gastroscopy was of great value in the study of patients who had undergone operation on the stomach and subsequently had had gastric distress. In my opinion, this is one of the most useful fields for gastroscopy.

The sources of error in the twenty cases in which the gastroscopic interpretation of the character of the gastric lesion was incorrect are given in table 2. In two of the cases, gastroscopic diagnosis was impossible owing to unsatisfactory visualization of the interior of the stomach because of accumulation of secretion and bleeding. Probably the most surprising finding was that in three instances the result of gastroscopic examination was reported as negative when gastritis was found at operation. This result at least demonstrates what was referred to earlier, namely that my colleagues and I insist on seeing definite changes in the gastric mucosa before making a gastroscopic diagnosis of gastritis. In three cases, a gastroscopic diagnosis of gastric ulcer was made, and at operation the condition was found to be one of ulcerative

TABLE 1
100 cases of proved gastritis

GASTROSCOPIC DIAGNOSIS		NO PREVIOUS OPERATION ON STOMACH	PREVIOUS OPERATION ON STOMACH
Correct.....	80	42	38
Wrong.....	20	19	1
Total.....	100	61	39

TABLE 2
Gastroscopic diagnosis in twenty cases of gastritis in which gastroscopy had been in error

DIAGNOSIS	NUMBER
Carcinoma.....	12
Ulcer.....	3
Negative.....	3
Indeterminate.....	2

gastritis. This is an error that may be extremely difficult to avoid. The most frequent source of error was in distinguishing gastritis from carcinoma of the stomach. In twelve of the cases the condition was misinterpreted as being due to carcinoma of the stomach. Obviously, this is a mistake that is deserving of the most careful consideration, because of the marked difference in implications that the two diagnoses involve. In referring to the study of 100 cases of proved cancer of the stomach, it was stated that in eleven cases the condition had been mistaken for gastritis. These results mean that there is an error of approximately 10 per cent in distinguishing between gastritis and carcinoma of the stomach.

The type of carcinoma of the stomach most likely to be confused with gastritis, as Schiff (7) has pointed out, is the linitis plastica, or leather bottle type. In this type of carcinoma, the difficulty is due primarily to the fact

that the lesion may involve the entire gastric mucosa, and as a consequence there is no normal mucosa present as a basis for differentiation by the gastroscopist. A carcinoma localized in a gastroscopically blind region will lead of necessity to difficulty in diagnosis. However, this is a rather uncommon occurrence and one that can be used too freely to cover an error in diagnosis. The greatest difficulty exists in those cases in which the carcinomatous process is submucosal in origin and limited to a rather small region and in which there is no associated tumefaction or ulceration. That the differential diagnosis is extremely difficult in certain cases is attested by the fact that in six of the cases of proved gastritis the surgeon, at the time of operation, experienced difficulty in determining whether the gastric lesion was benign or malignant, and the final diagnosis had to rest on microscopic examination of the gastric tissue. Case 1 is of this type.

Case 1.—The patient was a woman, forty-nine years of age, who had been perfectly well until two years before coming to the Mayo Clinic for examination. At that time, she began to have dull, aching pain in the right lower quadrant of her abdomen. This was noticeable chiefly during the daytime and was especially aggravated by nervousness. There was no relationship to eating, either of a quantitative or of a qualitative nature. There was no associated nausea, vomiting or disturbance in her intestinal habits. Six months before our examination she began to have intermittent attacks of epigastric pain which would appear while she was eating. The attacks were especially likely to occur at luncheon and at dinner; she had no difficulty at the morning meal. The pain never awakened her at night and there was no associated nausea, vomiting or hematemesis. The patient did belch a great deal and this seemed to afford her some relief. Her symptoms were definitely aggravated by nervous tension. She had been on a reduction type of diet and during the period of two years had lost approximately 50 pounds (22.7 kg.). A roentgenogram of the stomach had been made elsewhere and this had been reported as showing a lesion at the outlet of the stomach.

Our physical examination gave essentially negative results. The pertinent laboratory findings were as follows: Analysis of gastric contents showed no free hydrochloric acid. Roentgenographic examination of the stomach was reported as showing a duodenal ulcer with diffuse narrowing of the distal third of the stomach; there was no associated palpable mass (fig. 1*a*). Flocculation reactions were negative. On gastroscopic examination, infiltration was observed to be present in the antral portion of the stomach. The gastric mucosa was thickened and nodular in appearance. Peristaltic waves, however, were found to pass through this region of involvement without difficulty, and when the abdominal wall was palpated while the gastric mucosa was being inspected through the gastroscope, the wall was found to be pliable. The region of involvement extended from the lower portion of the antrum up to just beyond the angle of the stomach. From the gastroscopic standpoint, the condition did not appear to be neoplastic. Operation was advised.

At the time of operation, infiltration was noted in the prepyloric portion of the

stomach. The exact nature of this infiltration could not be determined. Because of the possibility of its being malignant partial gastrectomy was performed and a posterior Polya anastomosis was made. On microscopic examination the region of involvement in the antral portion of the stomach was found to be due to chronic ulcerative gastritis involving the distal 8 cm. of the stomach, with associated patchy ulceration of the mucosa and marked infiltration of the wall. This was classified as ulcerative gastritis, grade 4 (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe gastritis) (fig. 1*b*).

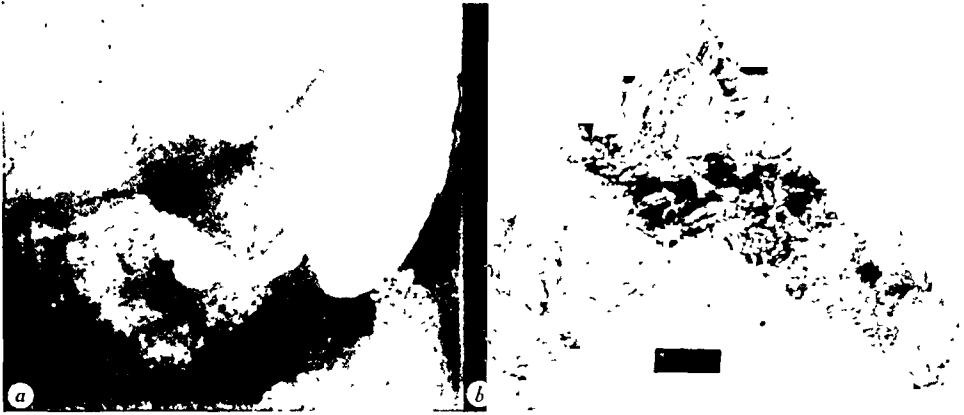


FIG. 1*a*. Stomach in case 1, demonstrating diffuse narrowing of distal third of the stomach. *b*. Resected portion of stomach in case 1, demonstrating area of gastritis.

When this patient was re-examined four years later she had had no recurrence of her gastric disease.

Considerable help by roentgenographic examination of the stomach is to be anticipated in the differential diagnosis of carcinoma of the stomach from gastritis. In cases of carcinoma of the stomach, the roentgenologist is able to furnish considerable assistance in the establishment of a correct diagnosis but even here, as Kirklin and I (5) pointed out, difficulty may be experienced in distinguishing between carcinoma and gastritis. With respect to gastritis itself, Gaither and Borland (8), Renshaw (9), and Templeton and Schindler (10) have stated that roentgenographic examination of the stomach is of little or no value in diagnosis. Berg (11), however, expressed the opinion that roentgenographic examination of the stomach could be of value in the diagnosis of gastritis. In reviewing the roentgenographic findings in the present series of cases of proved gastritis, it is of interest that the roentgenologist had made a diagnosis of gastritis in thirty-two of the cases. This is indeed an extremely commendable figure. The roentgenologic signs on which the diagnosis of gastritis was based are those described by Ansprenger and Kirklin (12). These consisted of the presence of localized, ragged, irregular hypertrophic mucosal

folds, or the presence of a wartlike granulation of the relief. These granulations appear as pinhead-sized or diffusely scattered wartlike lesions. One of the most indicative of the roentgenologic signs of gastritis is the demonstration of mucosal erosions.

From the gastroscopic standpoint, probably the most noteworthy fact is that in nine of the proved cases of gastritis the roentgenologist had requested the gastroscopic examination because of the unusual roentgenoscopic picture, feeling that there was insufficient evidence at hand to establish a definite diagnosis. This is a field that is deserving of cultivation. I feel certain that through such co-operation it will be possible to arrive at an earlier diagnosis of gastric lesions than would take place if this co-operation were lacking.

In some respects, error in gastroscopic diagnosis of carcinoma when the condition is gastritis is somewhat more justified than an error in the opposite direction, because if the condition should be diagnosed as carcinoma prompt surgical intervention would be indicated. If, on the other hand, carcinoma of the stomach should be misinterpreted as gastritis, the patient might be allowed to go untreated until the condition had reached a stage of inoperability.

Taylor (13) has called attention to the importance and value of repeating gastroscopic examinations to avoid errors in gastroscopic diagnosis. This no doubt may be of value at times in the same manner that repeated roentgenologic examinations of the stomach may lead to the correct diagnosis. There is, of course, also the possibility that a correct diagnosis may be altered to an incorrect one by re-examination. The following case well illustrates the difficulty that may be experienced in determining the nature of the lesion even on gastric exploration.

Case 2.—The patient was a man, forty-four years of age. He gave a history of having had a duodenal ulcer two years before coming to the clinic for examination. He had been placed on an ulcer diet with alkalies and had had a good response to this type of treatment. Roentgenologic examination of the stomach four months prior to our examination had been reported as giving negative results. Two weeks before his coming to the clinic, there suddenly developed in the epigastrium an ulcer type of pain which was relieved by food and belching. He had no tarry stools or hematemesis. During the few days before our examination the distress had increased in severity and had been associated with vomiting.

General physical examination was found to give essentially negative results. On analysis of gastric contents there was no free hydrochloric acid; the total acidity was reported as 6 units at the end of one hour and there was considerable retention. The first roentgenogram taken of the stomach was unsatisfactory as the patient was unable to retain the barium meal. On reexamination the roentgenogram was reported as showing a duodenal ulcer with considerable edema of the mucosa of the distal half of the stomach, suggesting gastritis. Gastroscopy was attempted but it

was impossible to complete the gastroscopy because the patient complained of so much gastric distress when an attempt was made to inflate the stomach with air. Roentgenographic examination was then repeated and reported as showing an ulcerating carcinoma of the distal third of the stomach (fig. 2*a*). Gastroscopy was again attempted and this time it was possible to complete the examination. This revealed edema about the distal third of the stomach with evidence of gastritis.

In view of the roentgenographic findings operation was advised. At the time of operation, the patient was found to have a lesion involving the lower third of the stomach, forming a mass approximately the size of a fist, 10 to 12 cm. in diameter. There was a great deal of shading of the mass into the gastric wall. It was impossible to say whether this mass was due to carcinoma or to gastritis. Partial

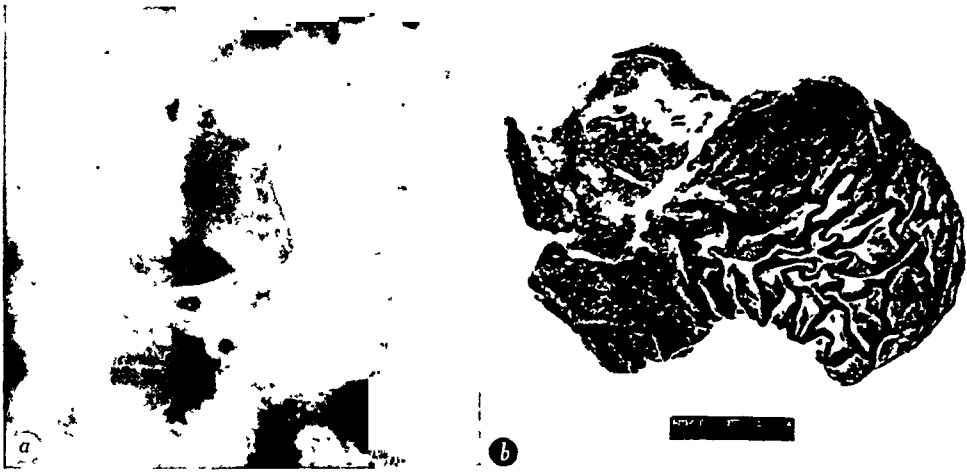


FIG. 2*a*. Lesion in case 2, reported as an ulcerating carcinoma of the distal third of stomach. *b*. Resected portion of stomach in case 2, demonstrating chronic ulcerative gastritis.

gastrectomy was done and a posterior Polya anastomosis was established. The gross specimen is shown in figure 2*b*. On microscopic examination the lesion was found to be chronic ulcerative gastritis, grade 4, which the pathologist reported was the most extensive that he had ever seen.

The patient's symptoms were completely relieved by the operation and he has had no further difficulty.

In passing, it might be mentioned briefly that a history of bleeding is not of a great deal of assistance in distinguishing between gastritis and carcinoma of the stomach. As Benedict (14) has pointed out, the presence of blood in the stomach is frequently associated with gastritis, especially gastritis of erosive type.

COMMENT

It is obvious that gastroscopy is not infallible in distinguishing between gastritis and carcinoma of the stomach. The usual characteristic pictures of carcinoma of the stomach and gastritis are well known and have been

repeatedly described in excellent articles that have appeared in the literature in recent years. I shall not attempt to repeat these descriptions here. I should like, however, to stress a few of the diagnostic aids that may be of assistance in distinguishing between these two lesions. It has been my observation that a frequent cause for error in gastroscopic diagnosis is an attempt to have the gastroscopic findings correspond to the clinical history. It is far better to report what is actually seen through the gastroscope than to try to read into the picture what would best agree with the clinical impression. Care is especially required in evaluating gastric lesions that are covered with secretions, and it is important that the stomach be as thoroughly empty as possible to avoid overlooking small lesions. Whenever difficulty is experienced in advancing a gastroscope after it has once entered the stomach, the possibility of a gastric tumor should always be seriously entertained.

Probably one of the best and briefest descriptions of the differential diagnosis between carcinoma of the stomach and gastritis is that which appears in Schindler's (15) textbook, as follows: "The nodules of the surface of a benign tumor are regular, granular and rather uniform in size, whereas in malignancy they are irregular and variable, some very large and some small. In hypertrophic gastritis the nodes are not so stiff and no solid tumor-like protrusion is observed."

Ruffin and Brown (16) have called attention to the influence of overdistention of the stomach in the diagnosis of gastritis. If one bases the diagnosis of gastritis on the character of the gastric mucosa rather than on the presence of gastric folds, there is little likelihood of error occurring in the diagnosis of gastritis based on overdistention of the stomach. Inflation of the stomach, however, can be of considerable aid in distinguishing between gastritis and carcinoma of the stomach, inasmuch as a carcinomatous lesion will not flatten out on overdistention of the stomach, as may occur in gastritis.

One of the most valuable aids in distinguishing between gastritis and carcinoma is palpation of the abdomen while examining the interior of the stomach through the gastroscope. By this means it is frequently possible to bring into view a lesion which otherwise might not be visualized, and it is often possible to determine whether the lesion is pliable or not. If it is pliable, it is more likely to be due to gastritis than to a carcinomatous process. Furthermore, palpation of the abdomen frequently will stimulate peristaltic activity which otherwise might not be present, and such peristaltic activity also may be of value in assisting in the differential diagnosis of the two lesions. Change of position is likewise to be advocated as assistance in this respect.

It must be remembered that gastritis and carcinoma of the stomach may coexist, and care must be exercised to carry out a complete and thorough examination in every case and the physician must not be misled in the interpretation by simply observing one portion of the stomach. The most important factor

of all is that the gastroscopic examination be carried out as carefully and completely as possible.

CONCLUSIONS

Gastroscoy is of value in the differential diagnosis between carcinoma of the stomach and gastritis. It is not, however, infallible and up to the present time an error of approximately 10 per cent has been experienced in distinguishing between the two lesions. It is better, however, to err toward a diagnosis of carcinoma than toward one of gastritis, as the patient is less likely to be allowed to go an undue length of time without proper treatment. Close co-operation between the roentgenologist, the clinician and the gastroscopist is to be highly recommended to enable the patient suffering from gastric disease to receive the most prompt and efficient care.

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DISCUSSION

DR. BENEDICT: I see Dr. Palmer leaving, but I want to ask him a question. You talked yesterday about the operations you performed. Were they done with the idea that the disease was probably cancer and it turned out to be gastritis, or am I misinterpreting?

DR. PALMER: The operations I mentioned yesterday were carried out with the thought that the lesion present was a carcinoma, but was found to be hypertrophic gastritis.

Dr. Stout's picture interested me very much in that connection. Two of the stomachs I showed yesterday had a rather normal appearing gastric mucosa and two of them had a development similar to that in the last patient that Dr. Stout showed; in the one instance a cystic formation was present in the glands such as Dr. Stout showed.

In those operations we were not recommending total gastrectomy.

METABOLIC DISTURBANCES IN WORKERS EXPOSED TO DINITROTOLUENE DURING WORLD WAR II

LEMUEL C. MCGEE, M.D. AND HOWARD L. REED, M.D.

Wilmington, Delaware

THEODORE J. NEREIM, M.D.

Madison, Wisconsin

C. A. PLUME, M.D.

Succasunna, New Jersey

AND

ALEXANDER MCCAUSLAND, M.D.

Roanoke, Va.

Dinitrotoluene is used as a chemical stabilizer in the manufacture of certain types of smokeless powder. Symptoms and clinical findings found in workers exposed to dinitrotoluene in the manufacture of smokeless powder have been described in an earlier report (1). The incidence of complaints in this experience early in World War II was sufficiently high, involving 112 men out of a group of 154 workers so exposed during a twelve-month period, to call for the application of special measures to reduce the exposure. It was noted in the previous report that the more troublesome places of work on the smokeless powder lines were in the "D.N.T. Screening House" and in the "Coating House." The commonest complaints were those of dysgeusia, weakness and lassitude, headache, inappetence, nausea or vomiting, dizziness, and pain or paresthesia in the extremities. Pallor and cyanosis were found in a third of the group originally studied. Some degree of anemia occurred in nearly one-fourth of these workers.

In 1942 an effort was made to reduce the exposure to dinitrotoluene through the following devices: 1) Engineering changes in methods used for crushing and screening dinitrotoluene, 2) improved ventilation in the buildings where the compound is handled, 3) application of good personal hygiene practices (bathing, the wearing of gloves by workers, etc.), 4) better training and closer supervision of workers in the execution of their tasks, and 5) rotation of such workers to jobs without exposure every other week or for half of each month.

The provision of better ventilation and other alterations in the handling of dinitrotoluene furnished a working environment with atmospheric concentrations usually much less than one milligram of dinitrotoluene per cubic meter of air.

Between midsummer 1942 and midsummer 1945, 714 workers exposed to dinitro-

trotoluene under the above conditions were given medical examinations at intervals of two to four weeks. A review of the records from these examinations shows a marked reduction in the incidence of symptoms and signs of illness as compared to the findings from the study of 154 workers for the twelve-month period covering the latter part of 1941 and the first of 1942 (1). Dysgeusia was rarely complained of during the last three years. Complaints of weakness and headache were found in approximately ten per cent of the men as compared to an incidence of fifty per cent during the first year of production of smokeless powder for military use. There occurred a similar

TABLE 1
Symptoms presented by 714 workers in dinitrotoluene

SYMPTOM	NUMBER MEN AFFECTED	PER CENT OF TOTAL MEN EXPOSED
Headache.....	94	13.2
Weakness and lassitude.....	62	8.7
Inappetence, nausea, vomiting.....	57	8.0
Vertigo.....	57	8.0
Pain or paresthesia in extremities.....	56	7.8
Upper abdominal discomfort.....	53	7.4

TABLE 2
Signs presented by 714 workers in dinitrotoluene

SIGN	NUMBER MEN AFFECTED	PER CENT OF TOTAL MEN EXPOSED
Anemia.....	73	10.2
Cyanosis.....	62	8.7
Dermatitis.....	32	4.5
Tenderness of liver.....	29	4.1

striking reduction in complaints of inappetence, nausea and vomiting, vertigo, pain or paresthesia in the extremities, and related symptoms. The findings from physical examination and clinical laboratory studies showed noteworthy improvement: pallor was rarely observed, there were no further instances of hepatitis of sufficient severity to show jaundice or require hospitalization, cyanosis dropped from thirty-four per cent to less than nine per cent and anemia from twenty-three per cent to ten per cent.

Table 1 shows the incidence of the more prevalent complaints among workers in dinitrotoluene for the period 1942 to 1945. It should be pointed out that such symptoms are non-specific and are occasionally complained of by workers in a wholly non-hazardous occupation (however, an unselected sample of records of workers in other occupations has not shown as great a frequency

or severity of symptoms as is encountered in D.N.T. workers). Hence, all such complaints may not be taken as evidence of toxic effects from the chemical handled.

Such findings as anemia, cyanosis, dermatitis and tenderness of the liver (which was not present on previous periodic examinations), usually with slight enlargement, are more valid evidences of disease. Such signs continued to be found occasionally in dinitrotoluene workers even with the various protective measures used to limit exposure after July, 1942. The incidence of these findings for the last three years of World War II is given in table 2.

SUMMARY

1. By means of adequate ventilation, personal protective devices, rotation of workers in and out of exposure, and alterations in the methods of handling of solid dinitrotoluene, the hazard of intoxication from this compound in the manufacture of military powders was significantly reduced.

2. The improvement has been shown in a reduction of complaints and clinical signs which may be attributed to the effects of dinitrotoluene.

3. Headache and weakness were the most frequent complaints, a low-grade anemia and cyanosis the most frequent findings in workers exposed to dinitrotoluene in this experience.

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HEPATITIS FOLLOWING TRANSFUSION*

J. EDWARD BERK, M.D., Sc.D. (MED)

From the Gastro-Intestinal Sections, Tilton and Rhoads General Hospitals

INTRODUCTION

The widespread outbreak of post-vaccinal (yellow fever) jaundice which occurred early in the recent war (8) forcibly directed attention to blood and its derivatives as a means of transmitting hepatitis. It was almost inevitable after this experience with small amounts of serum that transfusions of large amounts of whole blood, plasma and serum should next become suspect. In 1943 a report of the British Ministry of Health (25) drew attention to twelve cases of jaundice which appeared after transfusion of blood or serum. Included among these were some of the nine cases subsequently reported in detail by Morgan and Williamson (33). In the same year Beeson (3) described seven cases of jaundice in civilians in the United States who had received whole blood transfusions from one to four months previously. Steiner (48), in 1944, described five cases of jaundice following transfusion of whole blood or plasma. On several occasions during that year, the author drew attention to the first of a group of such cases which had been encountered at the Tilton General Hospital (5). Subsequently, other observers in widely separated military hospitals (6, 14, 15, 34, 42, 43, 47) reported similar examples. As a result, post-transfusion hepatitis has come to be recognized as still another variety of infectious hepatitis.

Until such time as effective means are found to prevent the transmission of the icterogenic agent in blood or its derivatives, transfusion hepatitis will continue to be a problem. If the disease is finally to emerge in its true perspective, all experiences should continue to be reported. Accordingly, this communication has as its purpose the presentation of the clinical data in 43 of a total of 72 soldiers with hepatitis which was thought to have followed transfusion of blood and/or plasma.

MATERIAL

The following criteria were established for classification as post-transfusion hepatitis: (1) an unquestioned acute hepatitis with jaundice; (2) the receipt of blood and/or plasma within six months of development of jaundice; (3) residence in the hospital for a minimum of one month before the onset;

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(4) a "relatively afebrile, more or less insidious type of onset akin to that previously observed following yellow fever vaccine. Some patients were included whose clinical picture did not conform with the last criterion in all respects. They were considered acceptable cases because the circumstances attending their injury, particularly their long hospitalization in the United States, made the likelihood of their having acquired the naturally occurring form of the disease small indeed. From August 16, 1943 to November 6, 1945 (27 months) 72 soldiers who met these requisites were encountered by the author at two large Army general hospitals in the zone of the interior. Their ages ranged from 19 to 37 with an average age of 25.8 years. All but two had been given blood and/or plasma for battle wounds or for injuries otherwise sustained. In 41 of the cases in which the product received could be determined 7 (17.1 per cent) had been given blood alone, 11 (26.8 per cent) plasma alone, and 23 (56.1 per cent) both blood and plasma. Illustrative of the severity of their injuries and of distinct bearing on the hepatitis subsequently developed, was the large amounts of blood and plasma given. The quantity of whole blood ranged from 350 to 7500 cc. with an average of 1687 cc. per patient; the quantity of plasma ranged from 250 to 2250 cc. with an average of 756 cc. per patient.

Despite the criteria employed in their selection, proof is lacking that these cases are bona fide instances of post-transfusion hepatitis. The evidence upon which the diagnosis rested was entirely circumstantial. Yet, it seemed sufficiently convincing to make the assumption valid. To begin with, there was at no time an epidemic of hepatitis in the hospital. Secondly, all of the patients had been in the hospital for at least one month and most of them had been in the relatively protected environment of a hospital much longer than that. Thirdly, every one of the cases, with two exceptions, originated among the wounded or injured on the surgical wards. In the two exceptions the patients developed hepatitis while in a medical ward. Both of them, however, had received blood or plasma within six months, one for nephrosis and the other for ulcerative colitis. Finally, no secondary cases appeared in the wards in which these cases originated. Only one patient who had not received blood or plasma, and who had been in the hospital one month or more, developed hepatitis in the same ward in which some of these patients resided.

INCIDENCE

In the two year period from September 1, 1943 to August 31, 1945, 212 soldiers were discharged from the gastro-intestinal section with an established diagnosis of acute hepatitis. Of this group, 39 or 18.4 per cent met the above mentioned requirements for classification as serum hepatitis secondary to

blood or plasma transfusion. The frequency of serum jaundice in combat casualties who were given blood or its products has been estimated to be about 2 to 3 per cent (26, 42). Grossman, Stewart and Stokes (15), reporting from an amputation center in the United States, found an incidence of 9.5 per cent in those patients who had received blood or plasma. The incidence of hepatitis among traced recipients of pooled lots of plasma or serum is variable but tends to be even higher (2 to 57 per cent) (6, 14, 33).

ETIOLOGY

Transmission experiments in human volunteers indicate that the hepatitis producing agent in blood or serum is viral in character and of at least two main varieties or strains (19, 20, 30, 36, 39, 41). Both strains or forms of virus are remarkably hardy and resistant. The infectious hepatitis virus which Havens studied was able to withstand heating to 56° C. for at least one-half hour (17). The serum hepatitis strain which Oliphant investigated was capable of surviving drying in vacuum, storage for long periods in serum at 4° C., and heating to 56° C. for one-half hour in the dried state (40). MacCallum and Bauer found that the icterogenic agent which caused homologous serum jaundice in their volunteers could survive heating in a water bath for one hour at 56° C. and was still very active after storage at 0° C. for 14 months in the dried state (30). The serum hepatitis virus investigated by Neefe and his co-workers remained active after three and one-half years residence in frozen plasma (36).

PATHOLOGY

Pathologically, the several types of hepatitis are indistinguishable (9). The autopsy findings in the four fatal cases in the group reported herein resembled those described by Lucké in his classical study of the pathology of epidemic hepatitis (27). A noteworthy pathologic feature of post-transfusion hepatitis, however, is the appalling devastation in the liver. We were impressed, as were Snell and his associates (47), with the lack of any signs of regeneration or repair. The livers grossly were flabby, soft, and below normal in weight. The color was usually a homogeneous, dark, beefy-brown with some fine yellow streaking occasionally interposed. The surface was characteristically smooth and free of nodular areas (figs. 1, 2). Microscopically, the classical picture was one of diffuse lysis and destruction of the parenchymal cells of the liver, especially in the central and mid-zonal areas. Infiltrations of inflammatory cells, particularly in the periportal areas, were also uniformly present (figs. 3, 4, 5, 6).



FIG. 1. GROSS APPEARANCE OF THE LIVER FROM A FATAL CASE OF TRANSFUSION HEPATITIS.
WEIGHT 1000 GRAMS

The surface is smooth and free of gross nodular hyperplasia. The diffuse, beefy, brown appearance is well shown.

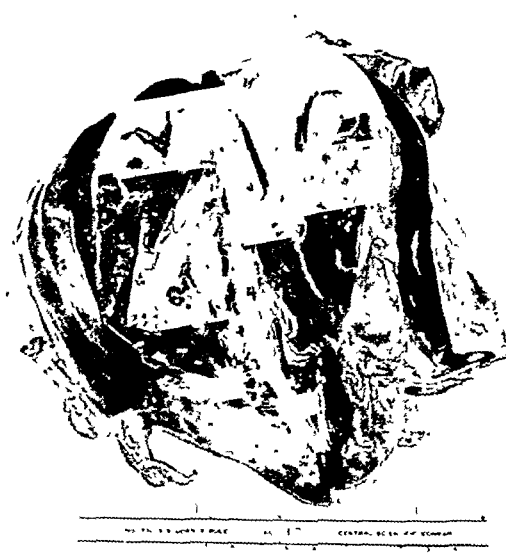


FIG. 2 GROSS APPEARANCE OF THE LIVER FROM A FATAL CASE OF TRANSFUSION HEPATITIS.
WEIGHT 1180 GRAMS

The organ was soft and flabby. Note the smooth surface and the absence of any suggestion of nodular hyperplasia or attempts at regeneration.

CLINICAL FEATURES

In the vast majority of our cases the clinical picture resembled much more that of serum hepatitis (12, 38, 50) than infectious (epidemic) hepatitis (16, 24). The incubation period as measured by the time intervening between the initial transfusion of blood or plasma and the appearance of jaundice (biliru-

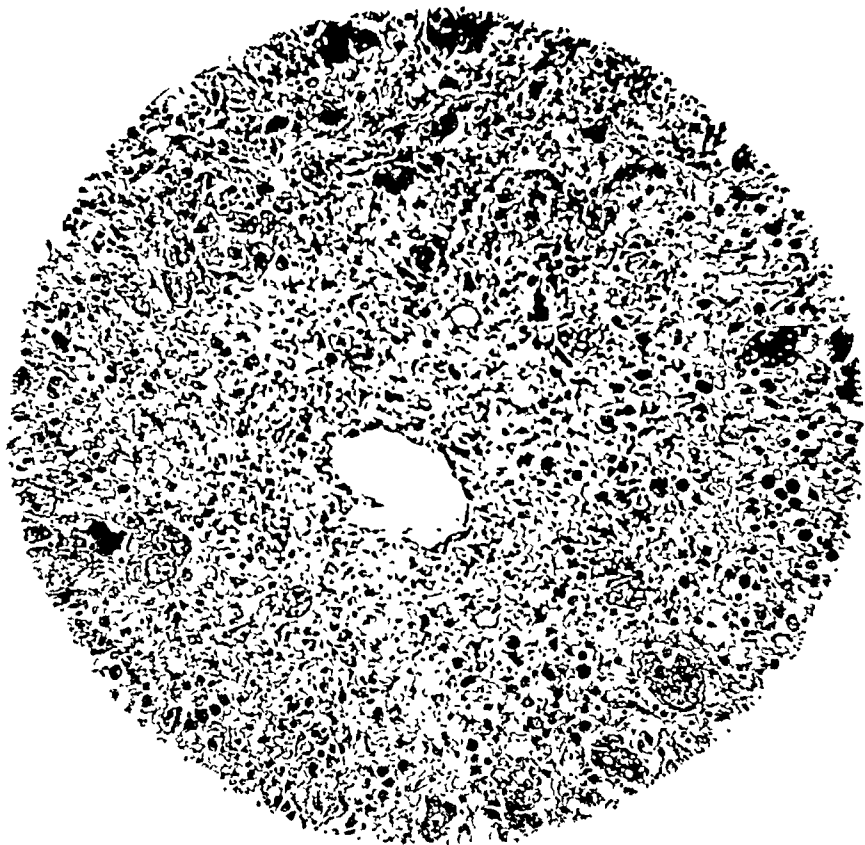


FIG. 3. PHOTOMICROGRAPH ($\times 200$) OF A SECTION FROM A LIVER WHICH WEIGHED 1420 GRAMS

The hepatic parenchymal cells in the inner two-thirds of the lobular are totally destroyed. A few viable hepatic cells are present at the periphery. The only elements which can be distinguished are erythrocytes, pigmented and non-pigmented Kupfer cells, hyaline debris, and infiltrates of inflammatory cells. The latter are limited largely to the portal radicals.

binuria or overt yellowing of the eyes or skin, whichever appeared earlier) ranged from 43 to 196 days with an average of 103.9 days; measured from the last transfusion to the clinical appearance of jaundice, the interval ranged from 38 to 196 days with an average of 95.7 days. The character of the onset in most of the cases was gradual, more or less insidious, and undramatic. The featured symptoms were anorexia, nausea, malaise, vomiting, and jaundice. Not infrequently, jaundice was the first symptom of note. An abrupt and dramatic episode with chills and fever was uncommon. Only 13 of the 43

cases whose records were available for review displayed a temperature of 100° F. (oral) or higher throughout the entire episode of hepatitis. If from this number there be omitted four who showed only a pre-agonal rise, and three others who had wound sepsis sufficient to account for fever, only six patients in the entire group (13.9 per cent) displayed fever of the degree stated.

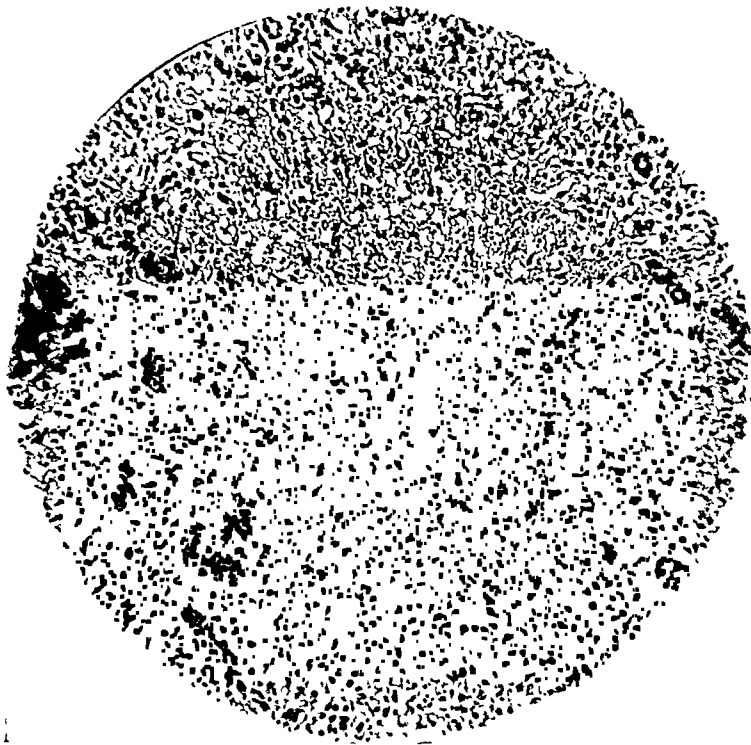


FIG. 4. PHOTOMICROGRAPH ($\times 200$) OF A SECTION OF THE LIVER SHOWN IN FIGURE 1

A small sublobular vein may be identified in the center of the section. There is a total destruction and disappearance of the hepatic cells. Details are obscured to a large extent by massive areas of hemorrhage. Many of the Kupfer cells persist and are heavily laden with a golden yellow pigment. At the periphery are numerous small bile ducts between which there is a periductal infiltration with inflammatory cells.

Snell and his associates remarked on the rare palpability of the liver and spleen in the early stages of transfusion hepatitis (47). Rappaport (42), on the other hand, noted hepatomegaly in all his cases without special note as to the stage of the disease in which hepatomegaly became apparent. He was able to palpate the spleen, however, in only one of 22 cases he observed from the onset of the disease. In the patients herein described, the liver was palpably enlarged in 60 per cent and the spleen in 22.5 per cent.

The severity of the disease appeared to bear no direct relationship to the

amount of blood or plasma received or to the number of transfusions given. There did appear to be some correlation between the severity of the disease and the age of the patient. Older patients tended to be jaundiced for longer periods and to require a longer time to recover weight loss and normal appetite and strength. In this regard, our observations are at variance with those of Rappaport. Several of our patients were desperately ill and some of them

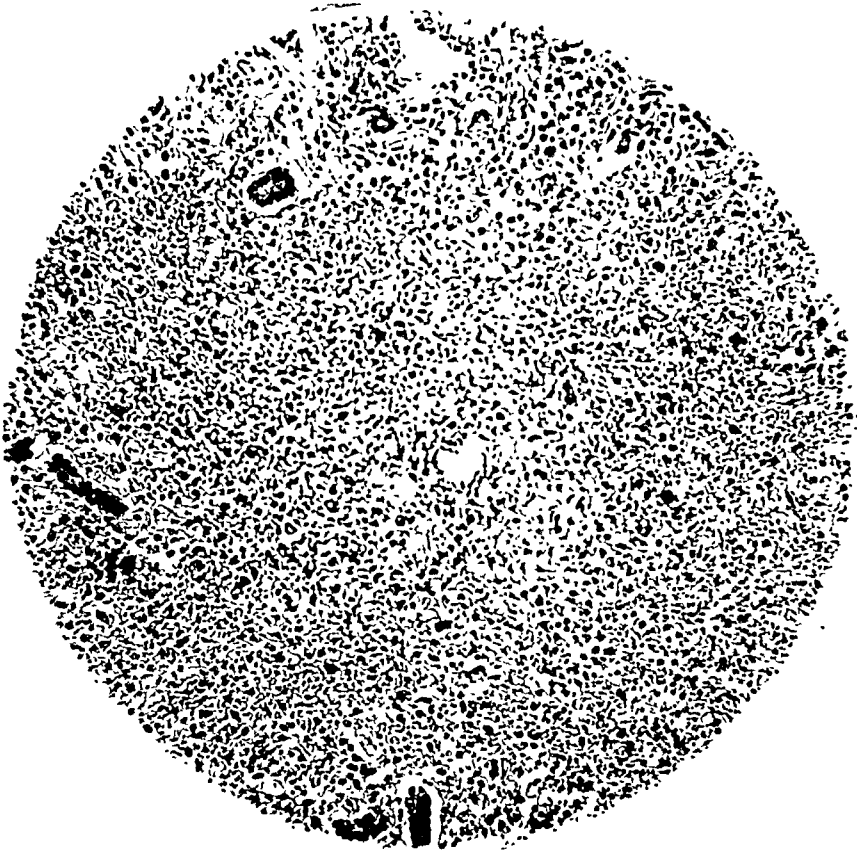


FIG. 5. PHOTOMICROGRAPH ($\times 200$) OF A SECTION OF THE LIVER FROM A FATAL CASE OF TRANSFUSION HEPATITIS. WEIGHT 920 GRAMS

A central vein is to be seen in the center of the section. The hepatic parenchymal cells have almost totally disappeared. The reticular framework is intact. In place of the polygonal cells is a collection made up of numerous erythrocytes, edema fluid, pigmented and non-pigmented Kupfer cells, monocytes and small numbers of neutrophilic leukocytes.

died. In this respect also, our experience is at variance with that of Rappaport, but is in harmony with that of Snell, Wood and Meienberg. A remarkable feature of the fatal cases, as noted also by Snell and his associates, was the rapid and inexorable progress of the disease. The duration of illness from the onset of the very first symptom to death did not exceed eight days and averaged 7.7 days. Nervous phenomena characteristically featured the terminal phase. Restlessness, delirium and then a wild mania was usually followed by stupor

and finally deep coma. Abnormalities in reflexes could commonly be demonstrated at this time, especially hyperreflexia, ankle clonus, and a positive Babinski's sign.

The duration of jaundice was variable. Measured from the appearance of the first detectable sign of clinical jaundice to the restoration of serum bilirubin to a level of 1.0 mg. per cent or less, the duration ranged from 8

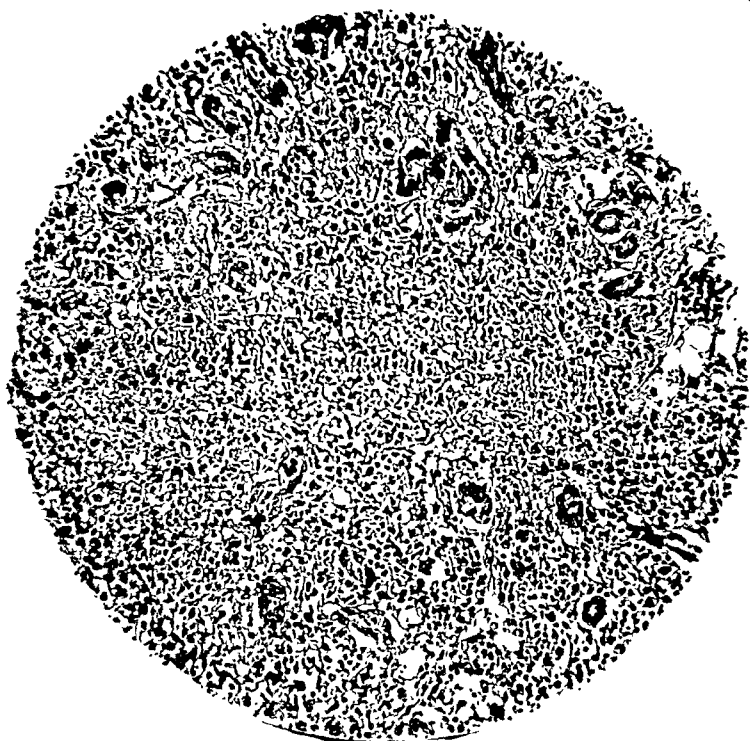


FIG. 6. PHOTOMICROGRAPH ($\times 200$) OF A SECTION OF THE LIVER SHOWN IN FIGURE 2

This consists in the main of a collapsed hepatic lobule. The hepatic parenchymal cells are wholly destroyed and have disappeared. Pigmented Kupfer cells and hemorrhage are present. In the periphery are numerous small bile ducts in the lumens of some of which are collections of neutrophilic cells.

to 94 days with an average of 35 days. In nearly all instances, the distressing symptoms of anorexia, nausea and malaise had completely cleared before the disappearance of jaundice. There was no apparent correlation between the amount of blood or plasma received and the duration of jaundice.

LABORATORY FINDINGS

The red blood cell count and hemoglobin concentration appeared to be little if at all affected by transfusion hepatitis. The white blood cell count

showed a distinct tendency to hover around the lower limit of the normal range or to descend into leukopenic levels. In the early acute phase of the disease there was both a relative and an absolute lymphocytosis. The highest observed white blood cell count throughout the acute phase of illness in this series of cases ranged from 4,400 to 13,300 with an average of 7,506 cells per cubic millimeter of blood. Differential analysis showed the polymorphonuclear neutrophils to comprise on the average 48 per cent of the white blood cells; large lymphocytes averaged 8 per cent, and the small and medium lymphocytes 33 per cent. Of notable interest was the occasional occurrence of large atypical lymphocytes identical with those seen in infectious mononucleosis.¹

The findings of such cells in the early stage of the disease made diagnosis more difficult. The danger of confusion between acute infectious hepatitis and infectious mononucleosis is further added to by the occurrence in some cases of hepatitis of a heterogenous antibody producing agglutination of sheep erythrocytes (11). Urinalysis was essentially negative save for occasional albuminuria in the early stages. Bile could usually be detected in the urine from one to three days before the clinical appearance of jaundice. Conversely, bilirubin usually disappeared before the return of the serum bilirubin to normal. Urobilinogen was present in increased amounts during the acute phase of the disease. A positive direct Van den Bergh reaction was invariably obtained when the serum bilirubin was elevated. The highest registered serum bilirubin in these cases ranged from 3.5 to 18.5 with an average of 7.9 mg. per cent; the icterus index ranged from 36 to 140 with an average of 77 units in those cases in which this determination was made.

Studies of liver function in infectious hepatitis indicate the existence of aberrations in practically all modalities during the acute phase (22). The greatest practical usefulness of liver function tests, as Hoagland and Shank (24) have pointed out, appears to be in the stage of convalescence. In twenty-five of our patients whose liver function was tested after the serum bilirubin had become normal, some abnormality was demonstrated in fifteen or 60 per cent. The most constant abnormality was an impairment in hippuric acid synthesis. Four patients showed abnormal retention of bromsulfalein but in none was this in excess of 10 per cent (2 mg./kg. dose with determination at 30 minutes).

TREATMENT

Prophylaxis: The ideal way to prevent transfusion hepatitis would be completely to eliminate the virus or viruses from blood, plasma or serum intended for therapeutic use. Ultraviolet irradiation of blood and plasma before transfusion (40) has not yet proved feasible. It is important, of course, to exclude

¹ Blood smears from unselected cases examined by Dr. Leandro Tocantins, Jefferson Medical College.

as a blood donor anyone with fever, jaundice, or a history of either (a) jaundice in the previous year, (b) exposure to infectious hepatitis within the preceding few months, or (c) transfusions of blood or plasma within a period of six months (19). If at all possible, blood, plasma or serum should be obtained from a single donor or at best from a few persons only (28). The evidence now accumulated pointing to the transmissibility of hepatitis through the use of improperly sterilized syringes containing minute amounts of contaminated blood (49), makes it mandatory to use individual sterile syringes for all routine venipunctures and intravenous injections.

The results to date with human gamma globulin in transfusion hepatitis have been conflicting. Grossman, Stewart and Stokes (15) reported a significant reduction in the incidence of hepatitis in the group of battle casualties to whom they gave 10 cc. of immune globulin on admission and again in one month. On the other hand, Robinson, Hamblin, Fleming, and Queen (44) and Duncan and his associates (10) found no significant reduction in the over-all incidence of hepatitis after the administration of a single dose of 10 cc. of immune globulin to wounded patients who had received blood and/or plasma. Gellis, Neefe and Stokes (13), in a preliminary experimental study could demonstrate no neutralizing effect by one preparation of gamma globulin on one strain of serum hepatitis virus. Ten cc. of gamma globulin was routinely administered to all battle casualties admitted to Tilton General Hospital on and after July 5, 1945. In the immediately preceding 246 days the average incidence of transfusion hepatitis was 1.3 cases per ten days; over the ensuing 133 days, the average incidence was 1.1 cases per ten days. It would appear from this that gamma globulin in these cases was without remarkable prophylactic effect.

Active: The therapeutic measures employed in the management of active cases of transfusion jaundice are identical with those used in hepatitis of other varieties. The details of the plan of management we employed will be described in another communication. Absolute bed rest, save for bathroom privileges, was insisted on until: 1, the serum bilirubin was 1.0 mg. per cent or less; 2, temperature was normal; 3, appetite had returned and the patient was able to take a full liver-type diet; 4, there was no tenderness on palpation in the right upper quadrant; and 5, preferably but not mandatory, the liver and spleen could no longer be felt. Physical activity was then increased at a rate dependent on the patient's tolerance. In many cases, however, progressive increase in physical activity was impossible because of the wound or injury for which the soldier had originally been hospitalized.

The best that could be done in the way of dietary care during the early stage of the disease when anorexia, nausea and vomiting were prominent, was to encourage the patient to take liquids or semi-solid foods of relatively high protein and low fat content, together with hard candies at frequent intervals.

During this stage glucose and protein solutions in the form of casein hydrolysate and plasma were given intravenously. Only rarely was a naso-gastric tube used for feeding purposes. As appetite improved the parenteral feedings were reduced and an attempt made rapidly to build up food intake by mouth. The diet finally offered the patient provided about 3,000 calories and was made up of 450 grams of carbohydrate, 150 grams of protein and approximately 60 grams of fat. We paid particular attention to the diet in wounded soldiers who developed hepatitis after transfusions because of their notoriously poor nutritional state (29, 32, 45). It is in these cases especially that human salt-poor albumin (46) should prove useful.

Vitamin supplements were given parenterally during the acute stage when the patient was unable to consume a full diet. These consisted of commercial preparations of vitamin B complex, sodium ascorbate, and crude liver extract (2 units per cc.). When the clinical condition had improved to the point where the patient was able to consume the regular liver-type diet, no supplementary vitamin therapy was employed save for a single commercial vitamin A-D concentrate. The latter was given because the diet was deficient in vitamin D and because most of the patients were confined indoors.

Choline chloride in enteric coated capsules was administered in a dosage of 1 gram three times a day to a few of the more seriously ill patients. Eight patients were given gamma globulin on an average of 6 days after the onset of symptoms. No ameliorating effect could be discerned in seven. The eighth patient had received 10 cc. of globulin two days before and again six days after the onset of symptoms. This patient was the only one in my experience to recover from hepatitis after progressing to the point of developing coma and other nervous signs.

PROGNOSIS

There were four deaths in the 72 cases comprising this series (5.6 per cent). Adding these cases to others in the literature (15, 21, 42, 47, 48) provides a total of 456 cases of post-transfusion hepatitis with 28 deaths or an average mortality of 6.1 per cent. Such a mortality is far in excess of that experienced to date in the other forms of hepatitis (0.2-0.3 per cent) (8).

Some patients with transfusion hepatitis may be expected to continue to have persistent distressing symptoms and objective evidence of liver derangement long after the acute attack has subsided (2, 4, 23, 31, 35). Rappaport noted that 16 of his 33 patients were still under observation 3 to 5 months after the onset of the disease with symptoms and clinical or laboratory evidence suggesting functional or morphologic alterations in the liver. It is noteworthy that 60 per cent of our patients showed some abnormality in liver function at a time when they were convalescent and no longer jaundiced. We had no

occasion to observe an icteric relapse or a recurrence of distress in these patients. It is important to point out, however, that many of them were confined to bed because of their wound. Even those who were ambulatory, with few exceptions, were limited to some extent in their physical activity. Had they been free to engage in full activity, a small percentage might have returned with a relapse or with a recurrence of distressing symptoms (1, 24).

DISCUSSION

Transfusion hepatitis is the most recent form of infectious hepatitis to be delineated. It is likely that the cases in this group are not separate entities but are related to the infectious and serum varieties of the disease. The evidence for this relationship, however, is still incomplete. Experiments in human volunteers have demonstrated that both the serum variety as well as the naturally occurring epidemic form of infectious hepatitis may be transmitted by parenteral inoculation of serum (19, 36, 41). Moreover, each viral agent, independent of the size of the dose or the route of entry, is associated with an incubation period and a clinical picture characteristic of the parent disease (17, 18, 19, 20, 36).

Murphy described the development of hepatitis in each of two soldiers who were transfused with blood from donors who subsequently developed hepatitis (34). Both donors seemed to have acquired the disease by natural means. The first recipient developed an abrupt febrile illness after 24 days; the second a more gradually appearing, relatively afebrile illness with jaundice on the 47th day. Oliphant's work (39) helps explain some of these variations. He obtained a virus from a spontaneously occurring case of jaundice in Italy which, on inoculation into human volunteers, behaved immunologically like the virus of serum hepatitis. It would seem, then, that not all cases of spontaneously occurring hepatitis are of the infectious (epidemic) variety; some, at least, are associated with the virus of serum hepatitis. Careful analysis of our own cases of transfusion hepatitis as well as those of others reported in the literature, reveals features characteristic of both infectious and serum hepatitis. The incubation period in some of the cases reported by Snell, Wood, and Meienberg (47) was well within the range for the epidemic variety. They described the development of hepatitis in a laboratory worker 19 days after the inadvertent ingestion of serum from one of their fatal cases. Two other of their laboratory workers with similar experiences developed positive cephalin cholesterol flocculation tests. The occurrence of hepatitis after an incubation period of only nineteen days suggests that the contaminated serum contained the virus of infectious hepatitis. The development of hepatitis after the oral ingestion of serum also favors an infectious strain of virus since it is difficult, if not impossible, to produce hepatitis in human volunteers by the oral ingestion of

serum hepatitis virus (36). It has yet to be proved by appropriate immunological studies (18, 37) that patients who have recovered from transfusion hepatitis are immune to subsequent infection with the virus of either serum or infectious hepatitis. When such information is finally obtained it should help considerably in clarifying the relationship between post-transfusion and the other forms of hepatitis.

The most impressive features of post-transfusion hepatitis are probably the amazingly rapid progression in those cases which terminate fatally, the heightened mortality rate, and the appalling devastation which occurs in the liver. It is highly debatable, however, if these features are inherent in the disease *per se*. Rather, it would seem, the process is more virulent and the destruction more widespread largely because of the depleted nutritional and protein state of those patients who require transfusions. Even before their injury many of these patients had, of necessity, been subsisting on substandard diets. After their injury, protein catabolism and malnutrition was undoubtedly present (29, 32, 45). Not only must there have been some diminution in their store of hepatic protein, but their resistance to infection must also have been impaired (7). In addition, many of them after their injury were further exposed to the ill effects of operative trauma as well as to such potential hepatotoxins as anesthetic agents and sulfonamides. One would expect, therefore, that hepatitis in individuals like these would prove to be of a more serious character. The important thing to remember is that transfusion hepatitis, probably because of the clinical status of the patient receiving the transfusion, is apt to be a very serious and treacherous disease.

There is little reason to doubt that many cases of sporadically occurring hepatitis among civilians are traceable to blood or plasma transfusions received several months previously. The long interval intervening between the transfusion and the development of clinical signs of hepatitis usually obscures the etiologic relationship. Follow-up studies of groups of cases who have received transfusions of blood or its products have disclosed numerous examples of jaundice which had been diagnosed as "catarrhal" (3, 6, 14). Until more effective prophylactic measures are available such cases no doubt will continue to occur, especially among patients receiving pooled plasma or serum to which large numbers of donors have contributed.

SUMMARY AND CONCLUSIONS

1. The data culled from the records of 43 of a total of 72 cases of hepatitis, considered on the basis of circumstantial evidence alone to have followed the administration of blood and/or plasma transfusions have been analyzed.

2. Hepatitis developing after transfusion of blood, plasma or serum appears to be related to both homologous serum hepatitis and infectious (epidemic) hepatitis. The evidence for this relationship, however, is still incomplete.

3. Post-transfusion hepatitis is associated with the greatest mortality of any of the groups of hepatitis thus far described. There is reason to believe that the more serious nature of transfusion hepatitis is ascribable not to the disease itself, but to the impaired protein and nutritional status of the patients who require transfusions.

4. Until more effective means of preventing or combatting the transmission of hepatitis virus in blood or its derivatives are devised, cases of transfusion hepatitis will undoubtedly continue to occur. All patients with sporadically occurring jaundice should be closely questioned regarding transfusions of blood, plasma or serum within a period of six months of the onset of the disease.

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EPIDEMIC HEPATITIS

EMMANUEL DEUTSCH, M.D. AND H. EDWARD MACMAHON, M.D.

From the Departments of Medicine and Pathology, Tufts College Medical School, Boston, Massachusetts, and the 16th General Hospital, United States Army

INTRODUCTION

It is the purpose of this paper to present: 1. simple methods of evaluation of liver damage in cases of acute and subacute infectious hepatitis, 2. the liver pathology in the only two fatal cases of a large epidemic, and 3. a simplified plan of treatment. The clinical aspect of this report is based on experience gained by one of us from a recent four months epidemic of acute hepatitis at a general hospital on the Western Front of the European Theatre of Operations. During this latter tour of duty, 267 officers and enlisted men were received because of epidemic hepatitis. A smaller group of unselected cases of this disease totaling 63, were retained for observation of clinical course and treatment. The majority of this latter group, under management to be outlined, exhibited a comparatively short phase of active infection and convalescence. They were soon able to return to full duty.

INCIDENCE OF CASES

These jaundiced troops came from various line units participating in the Battles of the Rhineland, Ardennes, and Central Germany. The chain of evacuation included a battalion aid station, an evacuation or field hospital and during the period 16 November 1944 to 10 June 1945 a total of 267 cases of jaundice were received. This figure includes all cases in which a final diagnosis of hepatitis was made. Thirteen cases were in colored soldiers. Table I shows the incidence of jaundice in American troops received at this hospital during the period described above. Beginning in January relatively large numbers of jaundiced non-battle casualties arrived at our tented general hospital which was being used as a large holding hospital for medical and surgical cases. March was the peak month with 94 cases. During May and June the epidemic had definitely begun to subside.

ETIOLOGY

The etiological agent of this diseases is unknown. Just preceding and concomitant with this epidemic of hepatitis moderately large groups of military personnel were hospitalized for protracted diarrhea of unexplained etiology, infectious mononucleosis, and primary atypical pneumonia. A hepatotoxic (icterogenic) filterable virus may be the cause of the disease (1, 2, 3, 4, 5, 5, 6, 7, 8, 9).

FATAL CASES

Of the entire group of 267 cases there were only two deaths, one fulminating case dying 7 days after onset of illness and one subacute case whose illness was followed for 40 days. Autopsies were obtained on both patients.

Case 1: A 27-year old white Technical Sergeant was admitted to the hospital on the 3rd of April 1945 complaining of general malaise and aching, headache, and vomiting of 3 days duration. His present illness began 3 days before entry and was characterized by headache, some coryza, generalized aches and pains, particularly in the low back, anorexia and persistent nausea and vomiting with inability to hold either solids or liquids. There was no diarrhea. Physical examination revealed a patient who appeared acutely ill and toxic. Temperature 99.4°F., pulse 90, respirations 20. There was some nasal congestion and his throat appeared injected. Except for some tenderness in the epigastrium, examination was otherwise negative. On the night of entry he was placed on combined chemotherapy (Penicillin 20,000 units every 3 hours intramuscularly and sulfadiazine in routine dosage) but he was unable to retain the sulfadiazine. On the following day he appeared more toxic and dehydrated. He then received 3000 cc. of 5% glucose in saline slowly intravenously. His temperature rose to 102°F. on the afternoon of entry but fell to normal on the 2nd day. On the evening of his 2nd day in the hospital, coffee-ground vomitus and icterus were noted. The liver was then noted to be enlarged one and a half finger breadths below the right costal margin. The next day the liver was one finger breadth below the costal margin, and was tender. Because of intermittent vomiting of coffee-ground material a Levine tube was inserted and approximately 200 cc. of coffee-ground fluid aspirated, a specimen of which gave a positive Benzidine reaction. One brown, formed stool was passed and this was negative for occult blood. The gastric tube was left in place for lavage and gavage every 4 hours. He was given 1 unit of pasma and 2000 cc. of 5% glucose intravenously, and penicillin was continued. During the early hours of 6 April he became incoherent and irrational and displaced the gastric tube. Paraldehyde in divided dosage intermuscularly and restraints were required. The pulse rate fluctuated between 85 and 115. The temperature and respirations remained normal. Neurological examination was negative except for transient bilateral grasp reflexes. The blood pressure was 80/40. Catheterization was necessary on 6 April and 900 cc. were obtained, part of this by voiding around and after the catheter as it was expelled. Thereafter he was incontinent. All attempts to intubate for feedings and medications were unsuccessful because of resistance on the part of the patient. In the early hours of April 7th and about 8 hours after his last dose of paraldehyde, pulmonary edema developed. The temperature, pulse and respirations which had been essentially normal on the 5th and 6th of April rose to 104.4°, 168, and 48 respectively. He slipped into coma, respirations became stertorous, and despite all supportive measures he died shortly after noon on his 4th hospital day.

Pathology: The liver (weight, 856 grams) was small, brown, soft and finely granular. Because the clinical signs and symptoms, laboratory procedures, management

and prognosis in infectious hepatitis are so intimately related to the finer changes in the liver, it seems warranted at this time to go into the histological changes in this and in the subsequent case in considerable detail.

Microscopic examination: The liver (fig. 1) is very, severely damaged. There are no lobules, there are no trabeculae, there are no cells in any part of the section that can be identified as liver cells. The portal areas and central veins are still recognizable. The space between these is reduced considerably and is made up of a somewhat collapsed and poorly defined, reticular framework, embedded in fluid and cellular debris, and infiltrated with few red blood cells, together with pigmented and

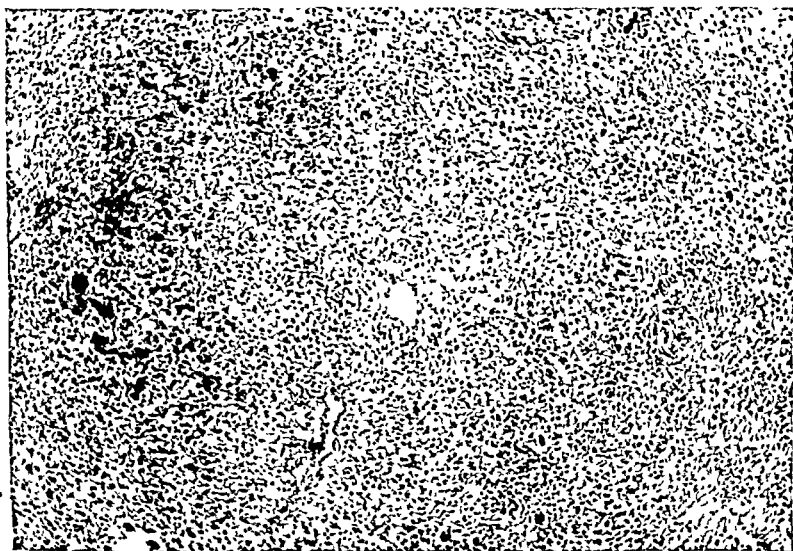


FIG. 1. (CASE 1) LOW POWER MAGNIFICATION OF LIVER

In the center of the field there is a distended empty central vein. This is surrounded by lobular tissue in which not a single liver cell is demonstrable. The bordering portal areas, five in number, are obscured by an inflammatory infiltration. The area between portal areas and central vein is filled with fluid, debris, swollen reticulum, few histiocytes and desquamated Kupffer cells.

non-pigmented histiocytes. It is difficult, and often impossible, to distinguish the sinusoids from the inter-sinusoidal spaces. Though the portal areas are demonstrable, they are poorly preserved and vaguely defined. They are represented by little edematous connective tissue, bile ducts, dilated and empty veins and here and there, a recognizable artery. In all portal areas, there is a cellular infiltration that varies both in character and in intensity. Most of these cells are monocytes, but there are lymphocytes, plasma cells, polymorphonuclear leucocytes, and an occasional eosinophil. The pattern of the small bile ducts is little changed, but the individual cells are not well preserved. Most of the ducts are collapsed and empty, but here and there, lumina are seen containing few polymorphonuclear leucocytes. In the zones between the portal areas and central veins, the cellular infiltration is much less con-

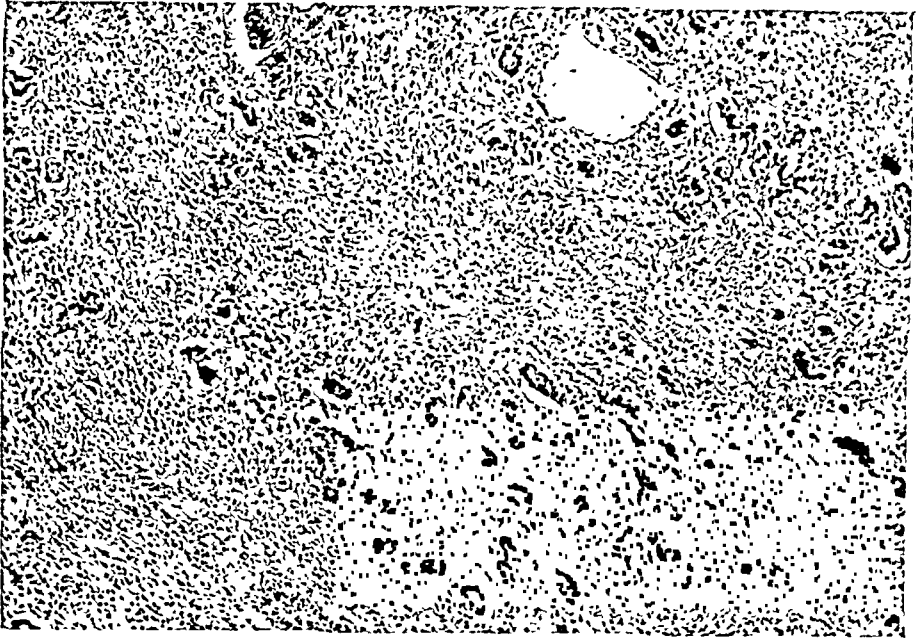


FIG. 3. (Case 2) LOW POWER MAGNIFICATION SHOWING IN THE CENTER OF THE FIELD A CENTRAL VEIN AND AT THE PERIPHERY TWO ABNORMALLY DILATED BRANCHES OF THE PORTAL VEIN

This entire field is made up of one complete lobule and portions of several others, as well as three portal areas. There is not a recognizable liver cell in the field. Because of the collapse of the lobules, a relatively large number of portal areas are visible in a single low power field.

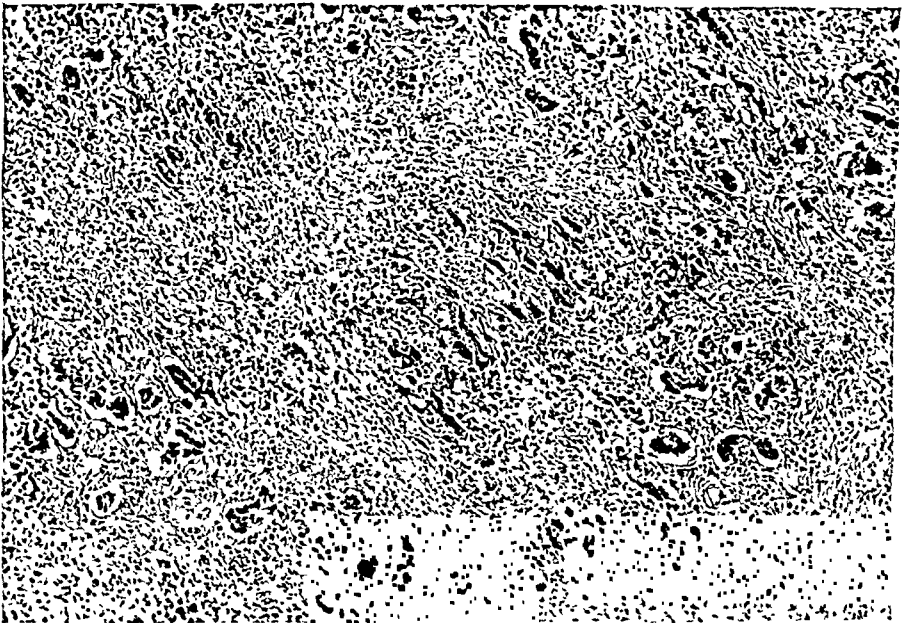


FIG. 4. (Case 2) LOW POWER MAGNIFICATION OF LIVER SHOWING IN THE CENTER OF THE FIELD A NEST OF SICK, DEAD AND CRUMBLING LIVER CELLS, ALL THAT REMAINS OF A LOBULE, BORDERED CENTRALLY BY A DISAPPEARANCE OF LIVER CELLS, AND, PERIPHERALLY, BY AN EXPANDING ZONE OF INTERSTITIAL INFLAMMATION CENTERED IN A PORTAL AREA

all other cells have disappeared, may show necrosis (fig. 4). Occasionally an entire lobule is necrotic. This change from the healthy cell to the sick cell to the dead cell is very simple,—at least histologically. The cytoplasm may stain more intensely or become diffusely discolored with bile. The nucleus stains less intensely and simply fades away and disappears. There is no vacuolization or hyalinization of the cytoplasm and the nuclei show neither shrinkage nor fragmentation. There is no sharp line distinguishing healthy cells from those that are sick and those that are dead. The transition appears to be gradual. Death of the cell is followed by what might be described as a process of crumbling, for the cytoplasm breaks up and seems to melt away. During this entire process of degeneration, necrosis and lysis, which apparently may take place in a very short time, there may be no cellular infiltration at all. Endothelial cells lining the sinuses in areas of liver cell necrosis sometimes persist and at other times they undergo the same sequence of changes as their adjacent liver cells. Red blood cells and leukocytes, often increased and lying within these sinuses, may undergo hemolysis and fragmentation. The necrosis and disappearance of the cells is followed by a light cellular infiltration of histiocytes, by little bleeding, and by the accumulation of considerable fluid both in the sinuses and trabecular spaces. This disappearance of liver cells in areas accompanied by collapse in the supporting stroma, naturally leads to a shifting and asymmetry of the lobular pattern of the liver as a whole. In older lesions, more cells,—histiocytes, lymphocytes, plasma cells and polymorphonuclear leucocytes may collect in the areas formerly occupied by cords of liver cells. In time, most of these inflammatory cells disappear. It must be emphasized again at this point that in this liver, areas of necrosis begin almost exclusively in the central zone and radiate from here into the midzones and peripheral zones of the lobules and that often the entire lobule is involved. Rarely one encounters in the peripheral or mid zone of an otherwise unaffected lobule an isolated liver cell or cluster of liver cells showing this characteristic type of degeneration and necrosis. Such cells may lie surrounded on all sides by healthy cells. This is an unusual finding but it is of some significance in showing that this type of cell death may take place in any part of the lobule and consequently need not of necessity begin in the central zone. This necrotizing process might well be described as one of *primary disseminated necrosis*.

The *second* and a very common finding is the picture of long-standing bile stasis (fig. 5). This is characterized by the retention of bile in liver cells,—especially those in the central zones of the lobule, by degenerative changes in these cells, by the accumulation of bile in bile canaliculi, by the appearance of an unusually large number of giant multinucleated liver cells, by hypertrophy and hyperplasia of Kupffer cells, by the accumulation of inspissated bile in the perisinusoidal spaces, by the phagocytosis of bile by Kupffer cells, by necrosis of isolated liver cells and by the accumulation in such areas of bile-staining histiocytes. The multinucleated liver cells may be several times as large as their neighbors. Their nuclei are alike in size and staining and are often clustered together in the center of the cell. Occasionally, one encounters an unusually large cell with an abnormally large single nucleus. Such giant nuclei may contain one or more round bodies suggesting

nucleoli. The changes in the portal areas are equally interesting. Here, there is a slight increase in the connective tissue, an elongation and tortuosity of bile ducts, an accumulation of bile in ducts, and a light cellular infiltration of polymorphonuclear leucocytes and occasional eosinophils. This overall picture comprising the changes within the lobule and in the portal area is similar to that of uncomplicated obstructive or cholestatic cirrhosis.

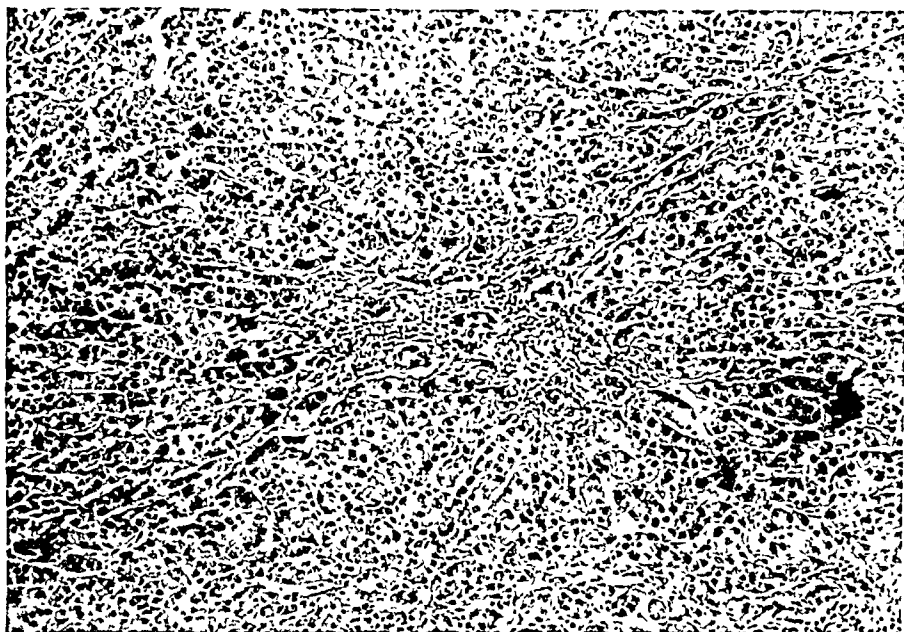


FIG. 5. (CASE 2) LOW POWER MAGNIFICATION OF LIVER SHOWING IN THE CENTER OF THE FIELD A SLIGHTLY WIDENED PORTAL AREA

There is an elongation, dilatation and tortuosity of small bile ducts, there is a slight increase in connective tissue and there is a light cellular infiltration. The adjoining lobules show intense bile stasis.

The *third* change, and one often combined with (1) disseminated necrosis and (2) bile stasis simulates the cholangelytic or infectious type of cirrhosis (fig. 6). This is characterized by an uneven and very appreciable widening of the portal areas at the expense of the liver cells in the peripheral zones of the adjoining lobules, by a lengthening and tortuosity of small bile ducts and in particular by a very definite increase in their number. These newly formed bile ducts vary considerably in size, in shape and in patency. Some are apparently devoid of lumina, others appear as drawn out, collapsed, lumenless, cords of cells. Others have lumina that are empty, some contain eosinophilic granular secretion, and others are distended with bile. There is dissociation, degeneration and necrosis of epithelial cells of both old and recently formed bile ducts; with this, there is extravasation of bile into the portal connective tissue. There are leucocytes about the ducts, in their walls and within their dilated lumina. At times, leucocytes and inspissated bile form obstructing grotesque casts. A very occasional mitotic figure is found in bile duct epithelium (fig. 7). A most conspicuous finding is a heavy, but variable infiltration

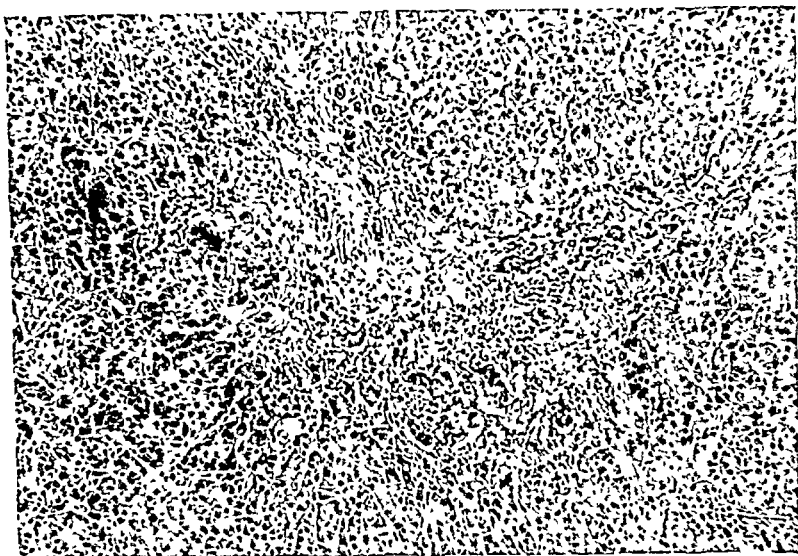


FIG. 6 (CASE 2) LOW POWER MAGNIFICATION OF LIVER SHOWING AN ENLARGED AND IRREGULAR PORTAL AREA

There is a great increase in small but poorly formed bile ducts, a condensation of reticulum and an increase in connective tissue and most striking, a heavy infiltration with cells. In this field most of the bordering liver cells are well preserved.

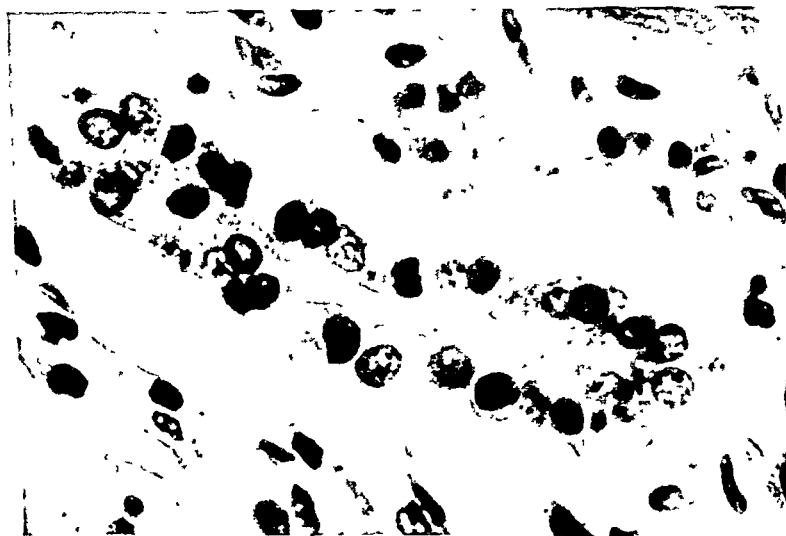


FIG. 7 (CASE 2) A HIGH POWER MAGNIFICATION OF LIVER SHOWING IN A SINGLE SECTION OF BILE DUCT FROM ONE OF THE PORTAL AREAS, TWO NUCLEI IN MITOSIS

The one, at the left, is in a very early phase; the other at about the center of the field appears as an equatorial plate, and one of the centrosomes and some of the spindle are visible. Both cells showing mitosis show a clearing of the cytoplasm. There is edema of the surrounding stroma.

of polymorphonuclear leucocytes, histiocytes, lymphocytes,—that sometimes accumulate in almost solid nodules, and plasma cells and eosinophils. There is edema throughout the stroma and in the nerves and in the walls of arteries. The veins and lymphatics are distended. There is a condensation of reticulum in the peripheral zones of the lobules and a slight increase in portal connective tissue. This whole series of changes is primarily an intersititial, inflammatory reaction. Changes in the adjacent lobules are of interest, often the liver cells are healthy and unaffected. In other areas the adjoining cells show shrinkage, over-staining

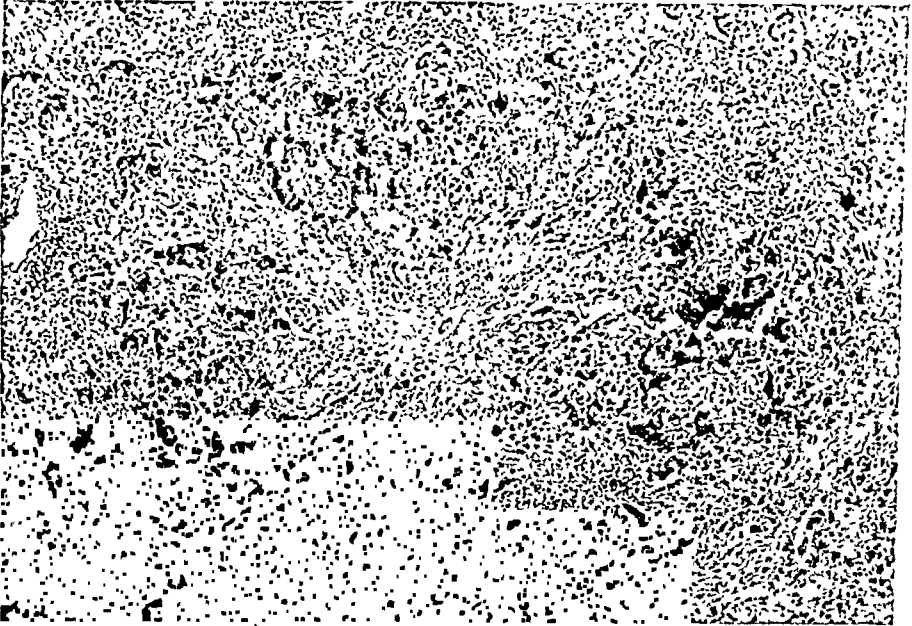


FIG. 8. (CASE 2) LOW POWER MAGNIFICATION OF THE LIVER SHOWING ALL THAT REMAINS OF A LOBULE

The few viable liver cells still show a poorly defined trabecular pattern. The central vein of the lobule is dilated. Liver cells from the central zone have disappeared. The peripheral zone is replaced by an expanding portal area. Note the intense inflammatory infiltration in the portal areas and its extension along the sinuses into the substance of the lobule.

and sometimes vacuolization. The nuclei of such cells are over-stained and shrunken. These cells die and disintegrate and leucocytes often infiltrate the bodies of these dead cells. Here and there, small nests or islands of liver cells become surrounded and cut off by spreading and infiltrating portal granulation tissue. No lobules appear to have undergone complete destruction simply as a result of this peripheral inflammatory reaction spreading out from the portal areas, but many times, viable liver cells singly and in small clusters lie flanked peripherally by an inflamed portal area and centrally by an area from which all liver cells have disappeared (fig. 8). Here and there, where expanding portal areas have reached out to join with spreading central zones and midzones of necrosis, entire lobules have been destroyed (fig. 9).

The *fourth* change (fig. 10), and one found only in areas of severe or complete lobular destruction, is characterized by swelling and edema of the walls of the central

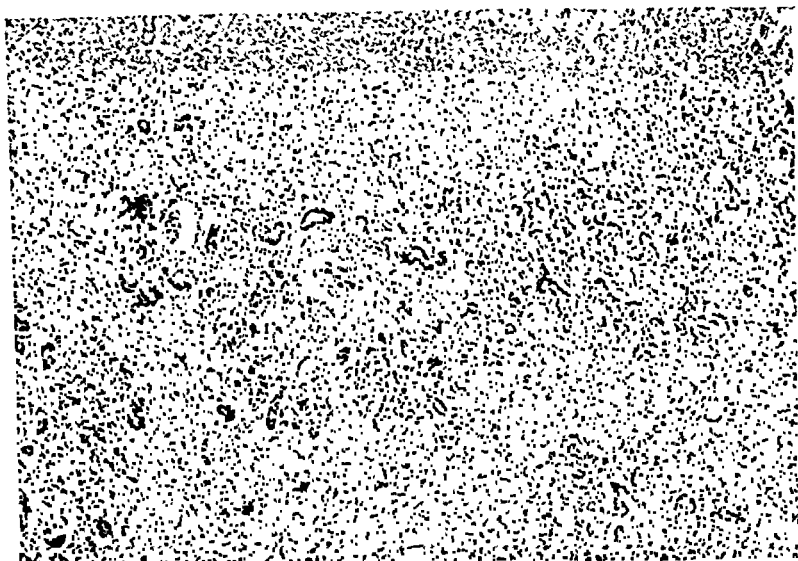


FIG. 9. (CASE 2) LOW POWER MAGNIFICATION OF LIVER SHOWING AREAS FROM WHICH ALL LIVER CELLS HAVE DISAPPEARED, BUT SHOWING ALSO A GREAT INCREASE IN BILE DUCTS AND BROADENING OF THE PORTAL AREAS

The central veins and portal areas in the field are dilated. The portal areas in contrast to the rest of the lobules show a heavy cellular infiltration.

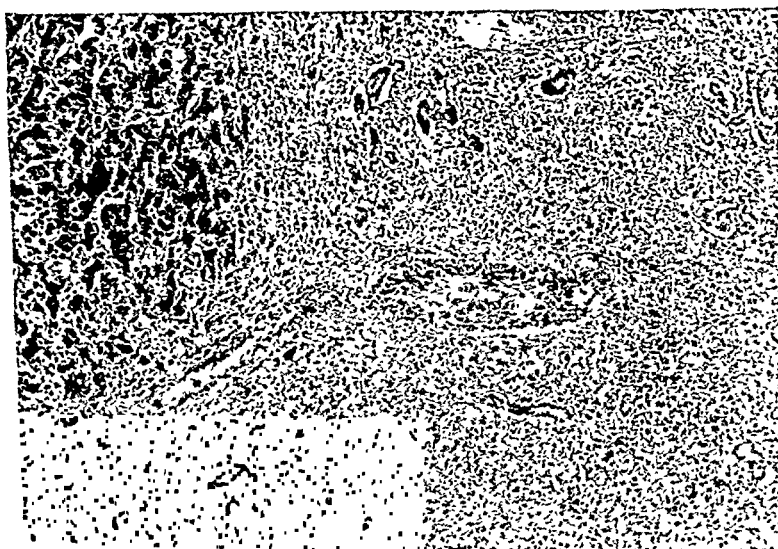


FIG. 10. (CASE 2) LOW POWER MAGNIFICATION OF SECTION OF LIVER SHOWING IN THE CENTER OF THE FIELD A CENTRAL OR SUBLOBULAR VEIN BORDERED BY AN AREA FROM WHICH THE LIVER CELLS ARE EITHER NECROTIC OR HAVE BEEN REMOVED

Of special interest is the swelling of the wall of the vein, the lifting up of the endothelial lining by an infiltration of inflammatory cells into the intima, and the consequent diminution in the size of the lumen.

veins, and by a subendothelial infiltration and accumulation of histiocytes, lymphocytes and polymorphonuclear leucocytes. This leads to an elevation of the endothelium, but nowhere is the lumen obstructed.

The *fifth* change, and one that is quite inconspicuous, is a variation in size of liver cells in different areas throughout the organ. There are first, the variations that are so commonly found in passing from the peripheral to the central zones of the lobules; secondly, there are the giant single and multinucleated liver cells that may be found singly and in clusters. Thirdly, there are many lobules, especially

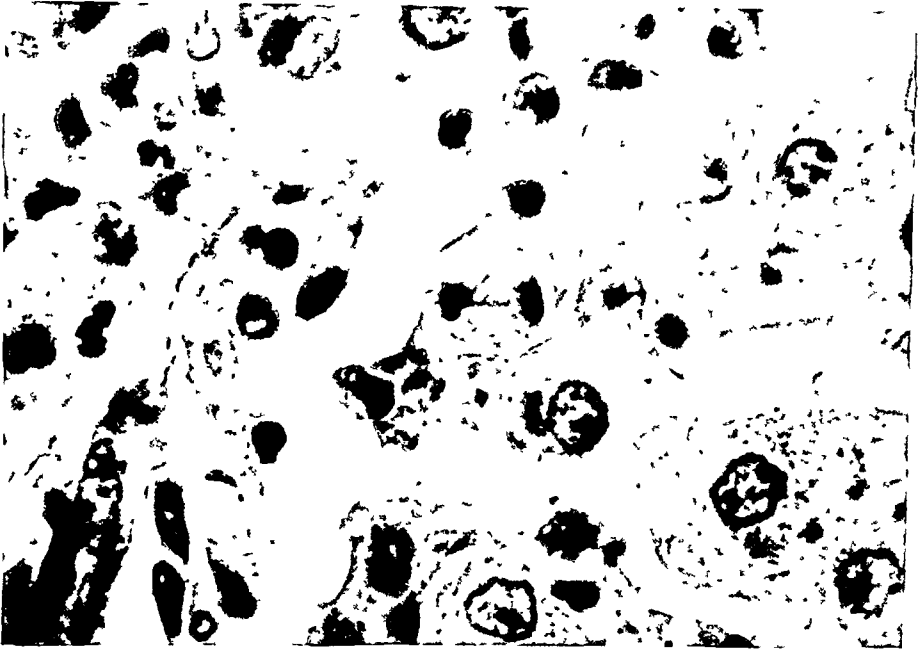


FIG. 11. (CASE 2) A HIGH POWER MAGNIFICATION OF THE LIVER, SHOWING IN THE CENTER OF THE FIELD A LIVER CELL NUCLEUS IN MITOSIS,—A DIASTER

Note the characteristic swelling and rounding up of the cell and its compression of the surrounding liver cells. This cell is just at the periphery of the lobule

near the capsule, that are entirely composed of large cells with a spumoid type of cytoplasm. Such cells are arranged in poorly formed cords but shade gradually over into the smaller cells that comprise the bulk of the liver. These larger cells show the same regressive changes and the same bile stasis as found in other areas. Mitoses are not found more commonly here than elsewhere.

The *sixth* change is one of liver cell regeneration (fig. 11). The evidence for this lies in the presence of mitoses. These are only rarely seen and in the sections examined, they are only found in the peripheral zones of the lobules.

The *seventh* finding involves the capsule. This change is not striking, and is simply an edema and light cellular infiltration resembling that found in many of the portal areas.

Microscopic diagnosis: "Subacute infectious hepatitis."

Comment: The overall picture is one of great destruction and little repair. It is obvious from the sections that changes have been taking place in this liver over a period of weeks,—and that at the time of death these changes were still active and progressing. It is equally apparent that, as a result of widespread destruction of liver cells, local disturbances in circulation and faulty elimination of bile, that the liver has reached a degree of injury incompatible with life. Of these seven changes observed in the sections,—all probably the result of a single etiological agent, two appear to be primary and the others secondary or dependent. The necrosis usually originating in the central zones and the interstitial inflammatory reaction in the portal areas, stand out above all others. Either of these may occur alone but their combination leading to partial or complete destruction of lobules is a common finding. The endophlebitis, the bile stasis, the proliferation of bile duct epithelium, and the regeneration and hypertrophy of liver cells appear to be subordinate findings (24). It is important to try to unravel this relationship, otherwise the pathogenesis of this complex picture remains obscure.

Bile stasis within the remaining lobules was such a striking feature of this case that it warrants special consideration. There can be little doubt too, that this played a significant rôle in the production of jaundice which was so conspicuous clinically. The histological picture of bile stasis is so obvious under the microscope but the means by which it may be brought about are not only variable but often obscure. In this case there was no extra-hepatic obstruction, nor was there any obvious blockage of any of the larger or medium sized intra-hepatic biliary ducts. Bile stasis was confined to those lobules whose corresponding portal areas showed an inflammatory reaction. In these areas there is an increase in newly formed bile ducts, many of which were incompletely and badly formed. The combination of relatively more bile being formed by the residual liver lobules and an inadequate and poorly formed terminal biliary system, probably represents both the site and the key to the mechanism of obstruction. In other words, the little remaining liver tissue together with a defective system of newly formed terminal bile ducts were simply inadequate to handle the increased output of bile.

The summation of all of these changes within the liver is great. The widespread destruction of liver tissue, the severe intra-hepatic biliary obstruction, the collapse of countless lobules, the blocking of large areas of portal circulation, combined with the local, regional and systemic manifestations of a subacute inflammatory reaction throughout the liver, form the morphological basis not alone for the complex clinical signs and symptoms, not alone for the diverse chemical changes encountered by the laboratory, but in this patient, for the mechanism of death.

CLINICAL EVALUATION

The degree of yellow color of the skin, sclerae and mucous membranes by itself is not often a good index of liver cell damage. The case of acute yellow atrophy cited above was only mildly icteric (icteric index 55 units). Listlessness, restlessness, apathy, delirium, lack of appetite and taste for soft or solid food, nausea, vomiting and coma are more important guides. The liver

after determination of the upper border of liver dullness was frequently one or two finger breadths enlarged downward in the right costal margin. The spleen was just palpable in approximately 5% of cases. Evidence of anemia, edema, telangiectasia, petechiae and gross vitamin deficiency was absent in all of the cases of this series. The diagnosis or evaluation of liver cell damage is best arrived at by the response to treatment. Search for spirochetes in the blood and urine was fruitless. There was no evidence of Weil's disease. None of these cases of acute infectious hepatitis required surgery. Twenty-seven soldiers ill with jaundice were admitted with a diagnosis of acute cholangitis, but on further clinical observation responded well to conservative management and fulfilled all the criteria of acute infectious hepatitis.

One soldier with moderate acute infectious hepatitis had been ill two and one half years previously with severe post-innocation yellow fever vaccine hepatitis. His course of illness and convalescence were uneventful. He was able to return to full duty with no untoward effects when last heard from.

Approximately one-third of these cases had noted diarrhea and associated cramp-like abdominal pain at the onset. About one-fourth of this series complained of an upper respiratory infection early in the disease. The remainder revealed no remarkable complaints referable to the onset of the illness.

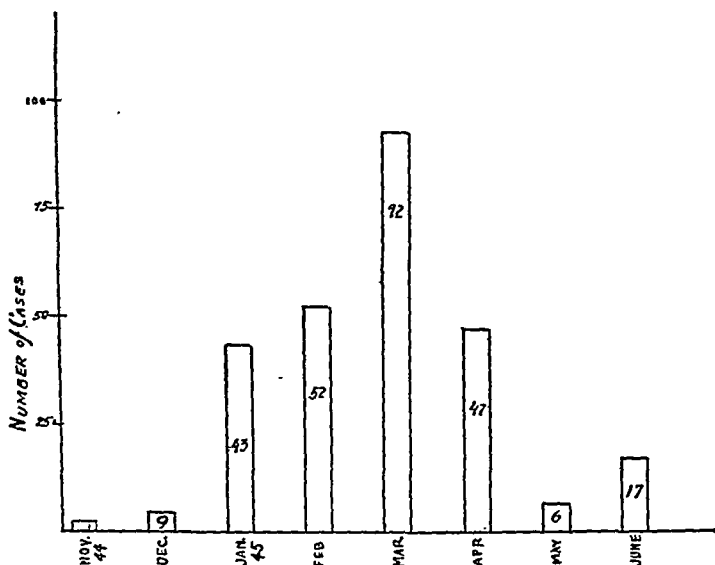
SIMPLE LIVER FUNCTION STUDIES

Simple single stage chemical tests (10, 11, 12, 13, 14, 15) were used so as not to overload the laboratory personnel during an epidemic. Tests requiring veni-puncture were avoided because in soldiers unable to take oral nourishment the veins had to be used for parenteral fluids. The only test requiring veni-puncture was the icteric index described in all text books of laboratory diagnosis. The normal limits for the icteric index in this series appeared to be 5 to 10 units. Values up to 350 units were recorded. The majority of cases fell in the range of 40 to 110 at the peak of illness. Bile in the urine was detected by the simple foam test. This index was found to compare favorably with the iodine interface reaction. The presence of bile in the urine was one of the earliest signs to appear at the onset of the illness and also one of the first to disappear in convalescence. This simple test aided in differentiating one case of congenital hemolytic jaundice from acute infectious hepatitis. With greater refinement, the value of the test for bilirubin in the urine is offset by detection of the pigment in normal urines. Approximately 3 per cent of the cases revealed albumen, bile, and formed elements in the urine consistent with bile nephrosis. However the non-protein nitrogen and protein fractions in the blood were within normal limits. Clinically these patients exhibited other evidence of a severe grade of hepatitis.

The test for urobilinogen in the urine of Wallace and Diamond (10) was

used routinely and one of these patients had a positive test above 1:20 dilution during the height of the illness or when well through convalescence. Elevation of urinary urobilinogen was frequent at the onset of the illness and at the beginning of convalescence. These elevations were usually in dilutions of 1:50 to 1:100. At the height of jaundice when stools are light tan or grey then the urine is usually urobilinogen-free or contains, at most, traces of urobilinogen up to 1:10 dilution. One or two days after the appearance of the first brown stool the secondary elevation of urobilinogen in the urine will occur. There-

TABLE I
Infectious hepatitis in American soldiers



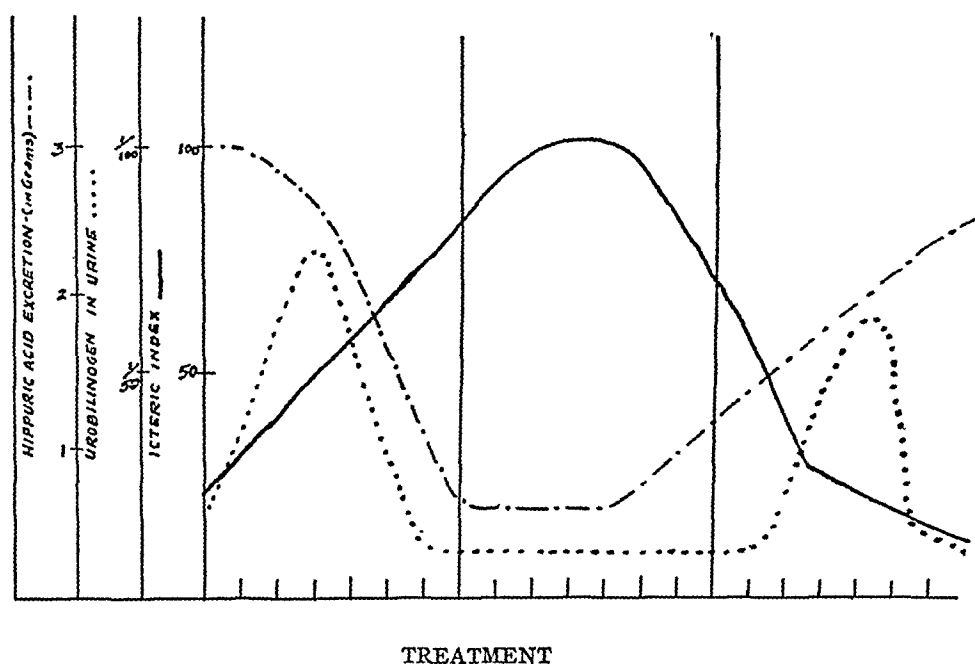
after convalescence is uneventful. The oral hippuric acid test was performed according to the technic recommended by Quick in 1936 (13). The dose of 6.0 grams of sodium benzoate was given in a glass of water one hour after a meal of tea and toast. The gravimetric method was used. An excretion of 2.5 to 4.0 grams was considered to be the normal range. Since there is an appreciable incidence of nausea and occasional vomiting after taking sodium benzoate this test was used in the main as a rough guide of residual liver damage, i.e. when the icteric index fell to less than 20 units. The fractional brom-sulfalein test (12) would have been ideal for this purpose but since the dye was unavailable in this theatre, the oral hippuric acid test made a satisfactory substitute.

A careful record of the fluid intake and output was kept with the purpose

of using a spontaneous diuresis as a fifth liver function test. The latter would indicate the onset of recovery phase of liver damage. Spontaneous diuresis was not a prominent feature in this series because none of these cases suffered a prolonged and severe enough bout of jaundice. None of the cases developed hypoproteinemia. The careful record of the fluid intake and output aided immeasurably as will be brought out later. The pattern of these simple liver function tests in a case of hepatitis with an acute phase of three weeks is indicated in Table II.

TABLE II

Diagram of function studies in a 3 weeks course of infectious hepatitis



Since the great majority of patients were able to eat very little of a solid or soft diet, the dietary had to be planned in liquid form. The plan of routine nourishment included 300–500 grams of carbohydrate, and 90–120 grams of protein daily. This was achieved by using ten per cent glucose in reconstituted powdered milk or dilute fruit juice drinks. The ten per cent glucose drink was the most palatable of a variety of concentrations tried. The reconstituted powdered milk, dilute fruit juice, and corn syrup (or glucose) was supplied to the ward personnel from the mess department. Ten per cent solutions were prepared in clean cast off intravenous fluid bottles. To each liter of fluid 8 tablespoonfuls of corn syrup was added. Routine feeding of three to four thousand cubic centimeters of milk and glucose per day easily fulfilled the basic requirements. Immediately upon return of the appetite this was

supplemented with a high carbohydrate, high protein, low fat diet. After recovery they were fed the normal diet for 2-4 weeks and then discharged to full duty. Shotgun excess vitamins were not used. In those cases of severe liver damage where utilization of glucose may be greatly diminished, large doses of thiamin, nicotinic acid amide and riboflavin were used. Vitamin K analogues were used daily in the same group of cases until the convalescent phase was reached.

Using the food values of milk as indicated by Bowes and Church (17) and the fact that one tablespoonful of corn syrup (light or dark) yields 15 grams of carbohydrate then 4000 cc. of reconstituted powdered milk with 10% glucose will provide in one day a total of 4144 calories. This total will include 644 grams of carbohydrate, 117 grams of protein and 122 grams of fat. Most of the patients were able to maintain this intake for at least 2 days. On the third or fourth day the total fluid intake was decreased to 3000 cc. of powdered milk. This was maintained along with supplementary feedings well into the convalescent period. With a total of 3000 cc. of powdered milk and 10% glucose, 3108 calories were ingested of which 483 grams were carbohydrate, 88 grams protein and 91 grams fat.

The carbohydrate intake was at least adequate if not abundant. Protein intake approached minimal levels, but the fairly large amounts of dairy fat were well tolerated. During convalescence about 30% of this entire series complained of indigestion following meals at the patient's mess which included gravies or other cooked animal fats. None noted any disturbance with dairy fats of milk, butter or cheese. A frequent comment at the end of convalescence was to the effect that a marked gain in weight had more than made up for that lost during the illness. No scales were available.

In very hot weather evaporated milk remained palatable for a longer time than did reconstituted milk. The contents of a one pint can of evaporated milk to which water is added to make one quart is equivalent in food values to a similar measure of reconstituted milk.

In the chain of evacuation from line units to the forward general hospital many of these sick jaundiced troops complained of increasing nausea on having to walk short distances to and from vehicles used in transportation. They frequently had to stand and wait for meals in long lines only to find that the regular army diet aggravated the usual degree of nausea and vomiting. The importance of bed rest can not be overemphasized. These soldiers were made bed patients on arrival at our hospital and given latrine privileges only. The soldier was encouraged to note his intake and output which was checked by the ward personnel and the ward officer. The simple liver function studies outlined above were repeated every 3 to 5 days. All this information was included on one improvised "Jaundice Work-Up Sheet". The very small

group of severely ill soldiers who were unable to retain a fluid diet were given frequent parenteral nourishment. Two to four units of plasma and 2000 cc. of five per cent glucose in normal saline solution were given daily until the appetite for fluid nourishment returned.

COURSE OF ILLNESS

Both the patients and ward personnel noted rapid improvement in the general well being of the patient, "washing out" of the icteric color of the skin and sclerae, improvement in appetite and strength. It was therefore an easy matter to maintain good morale on these wards, so much so that these soldiers frequently asked to be allowed to go back to duty prematurely.

The acute phase of active infection was arbitrarily regarded as the interval between ward arrival and the day the icteric index dropped to 20 units or less. If clinical appraisal of the patient indicated the onset of convalescence then the hippuric acid excretion was performed. In most cases at this point the latter test was within normal limits so the patients were then allowed to be up and about the ward for two to three days and then sent to the patient's mess.

The convalescent phase began with the end of the acute phase described above and continued until the soldier was ready for full duty. The duration of this period was usually two to three times the acute phase interval, depending on the severity of the illness. Thus if the icteric index dropped to 20 units or less in 7 to 10 days, as occurred in approximately 40% of the cases, then a convalescent period of three weeks proved clinically to be entirely adequate. Consequently in a considerable number of hepatitis cases one month's time may adequately cover both the acute phase of active infection and the convalescent period. Functional activity was gradually increased during the last half of convalescence to include one to five mile hikes. With no recurrence of hepatic tenderness, enlargement or positive function studies the patient was then discharged to full duty.

Three non-jaundiced soldiers were admitted for an ill-defined condition of the gastro-intestinal system characterized by nausea and vomiting. Because of abnormal results in two or more function studies associated with slightly enlarged and tender livers, these cases were termed "hepatitis without jaundice". They quickly recovered after one week of bed rest and the described routine and were able to return to full duty after a 2-week's convalescent period.

About 30% of the cases studied noted the onset of diarrhea a day or two after starting the milk and glucose diet. The diarrhea frequently persisted when dilute fruit juice was substituted for the milk. These patients were afebrile and exhibited only mild abdominal distension. Frequent stool cultures and examination for ova and parasites yielded only a normal intestinal

flora. The diarrhea would disappear on a soft bland diet. One explanation for this phenomena is that this diarrhea was fermentative in etiology since it disappeared when carbohydrate was reduced. In this latter group, the acute phase was prolonged by only a few days.

One of the complications of high glucose feeding is the stimulation of the pancreas to hypersecretion or hyperinsulinism. The danger of pulmonary edema associated with early morning hypoglycemia can easily be overcome if the nurse will awaken each jaundice bed patient early and offer him of the 10% glucose drink. No case of hyperinsulinism was observed in this group of cases.

Tonsillitis with peritonsillar abscess, carbuncles of the neck, and buttocks occurring during the acute or convalescent phase of infection were treated with full dosage of sulfadiazene and/or penicillin without untoward clinical effect or change in improvement of the course of tests.

SUMMARY OF TREATMENT

In brief, the following routine for jaundice patients was used at our hospital:

All obviously jaundiced patients were given a litter status. These patients remained in bed on the ward until the icteric index was 20 units or less. Every case of jaundice was regarded as potentially a case of acute yellow atrophy. Fluid intake of 4000 cc. of powdered milk and 10% glucose for the first two days, thereafter 3000 cc. of the same fluid daily until well into convalescence. Functional activity was increased when clinical and laboratory indices were at normal levels. (To mess, hike, pass to town.) Duration of convalescent period should be 2-3 times the duration of acute phase. When cooked fats such as gravies and/or pork permitted during convalescence caused indigestion, they were avoided. Dairy fats such as milk, butter and cheese were allowed. On discharge the soldier was cautioned against the use of alcoholic beverages including beer for at least six months and preferably one year. Full dosage of sulfadiazine and/or penicillin for indicated intercurrent infection was used without untoward clinical effect on the course.

DISCUSSION

If all soldiers with obvious jaundice were made litter cases from the beginning in the chain of evacuation, the acute phase of illness might well be shortened. Each soldier ill with jaundice should be regarded as a potential case of acute yellow atrophy. Then the giving of a high milk and glucose diet early in his illness might well result in speedier recovery from the acute phase of infectious hepatitis, and the convalescent period. His morale is much improved, and his return to full duty with his unit is hereby easily achieved.

In most epidemics the clinical picture has remarkable similarity and the

mortality has been low, ranging from 0.2 to 0.4 per cent (19). The mortality in this series is 0.7 per cent.

Total caloric, protein, carbohydrate, and fluid requirements were easily assured with the patient at rest. The relatively high level of dairy fat was well tolerated. The striking loss of body fat in a case of subacute yellow atrophy which was observed at necropsy suggests the need for fat in the diet of a "fat sparer".

The problem of the exact diagnosis of this condition clinically and at the autopsy table, is an important one. The variable histological changes encountered from field to field make the diagnosis during life by punch biopsy and needle aspiration alone uncertain. One field may show bile stasis, another central necrosis, another cholangiolitis, and still another acute diffuse necrosis. One section could show all of these, while another might show none.

A study of the histology of the livers from the two fatal cases clearly indicates the nature of the process underlying this epidemic form of liver disease. The fact that in the first case the duration of the disease was less than seven days and of the second, of about forty, might lead one to suspect that the two livers would have little pathological histology in common. Actually, while there are many differences, the two most significant lesions, namely widespread liver cell necrosis and active inflammation are common to both.

SUMMARY

A simple plan of observation and treatment of American soldiers ill with jaundice is presented. This was used to advantage during an epidemic of acute infectious hepatitis in an active theatre of operations. These troops were returned to their line units after relatively short periods of hospitalization without evident recurrences. The majority of cases exhibited a benign course. The course and pathology in two fatal cases of epidemic hepatitis are described. Histological studies show clearly the weakness of punch biopsy as a single means of diagnosis.

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AMEBIC LIVER ABSCESS IN SERVICE PERSONNEL

L. KRAEER FERGUSON, M. D. AND ROBERT KENT ANDERSON, M.D.
Philadelphia, Pa., and U. S. Naval Hospital, St. Albans, N. Y.

INTRODUCTION

Although amebiasis was for a long time considered a tropical disease, the investigations of Craig (1) and of Wenrich, Stabler and Arnett (2) have shown the disease to be widespread even in the northern parts of the United States. With the return of the armed forces who have been on duty in areas where the incidence of amebiasis is high, the appearance of the disease and its complications may be expected to increase.

From a surgical point of view, the most important complication of amebiasis is liver abscess. The incidence of this complication has varied according to the reports in the literature. Ochsner and DeBakey (3) find an incidence of 36.5 per cent in 4,994 fatal cases collected from the literature, and in the Charity Hospital the incidence of hepatic abscess varied from 15.2 to 20.4 per cent of patients with amebic dysentery. An impression is gained that hepatic abscess is even more common in the amebiasis of service men, especially those from North Africa.

The route of hepatic infection is via the portal system from the colon, with the development first of a hepatitis which progresses to a liquefaction necrosis of the liver tissue. Craig (1) has shown that amebae produce a lysis of hepatic cells. There first occurs then an hepatic necrosis progressing to the formation of a bloody, brown, "chocolate-sauce" liquefaction, a liver abscess. In the stage of hepatitis and early abscess formation, the most effective therapy is systemic emetine in doses of one grain daily for six to ten days.

Many abscesses progress, without recognition, to more serious complications. Perforation through the diaphragm to involve the pleural cavity is usually a late complication and was not seen in our cases. The more common complication is secondary infection of the abscess with pyogenic organisms. Frequently, the acute symptoms of a pyogenic infection are the presenting complaints. The time from the amebic colonic symptoms to those of liver abscess varied from one month to one year in our cases.

DIAGNOSIS

The diagnosis of hepatic abscess of amebic origin is not as simple as it might seem. A history of amebic dysentery is suggestive when it can be obtained, but this is not always easy. Many service men thought that an attack or two of diarrhea was to be expected in foreign climes and never reported their diffi-

culty. One of our patients developed his diarrhea returning home from Africa as a member of an armed guard crew on a merchant ship without a doctor. In others, in spite of repeated stool examinations, no *Endameba histolytica* were demonstrated and the diarrhea was attributed to food, drinking water or heat. The clinical signs, in the order in which they appear, are general malaise and loss of appetite, leading to a progressive loss of weight and a moderate anemia. Gradually, pain appears in the upper right abdomen and hepatic tenderness is found on examination. Intermittent fever is the rule, usually between 99° F. to 101° F. in uncomplicated abscesses, but rising to 103° F. and 104° F. in abscesses with secondary infection. Chills are likewise suggestive of secondary infection. The leucocyte count also varies with the presence or absence of pyogenic invaders. In simple amebic hepatitis and abscess, the count is usually low, whereas counts of 20,000 to 30,000 usually indicate secondary infection.

Unfortunately, the course of the disease is not always typical. Walters and coworkers (4) report two cases of liver abscess unsuspected until perforation. Furthermore, the diagnosis may not even be suspected. One of our cases was operated on for appendicitis, one for ruptured ulcer, one for pancreatic cyst and a fourth was treated for gallbladder disease. Roentgen examination is helpful in arriving at a diagnosis, especially in those cases in which the abscess is located in the dome of the liver. Elevation of the right leaf of the diaphragm, but without complete loss of diaphragmatic motion, is usual with simple amebic abscess. Elevation with loss of diaphragmatic motion and pleural reaction above the diaphragm may indicate secondary infection of the abscess or perforation into the subdiaphragmatic space. Abscesses arising deep in the right lobe or presenting on the lower surface of the liver do not show the characteristic unilateral diaphragmatic elevation.

OBSERVATIONS

There are certain clinical observations that may prove helpful in locating the site of the abscess. In abscesses presenting high on the lateral surface of the right lobe where the liver is covered by the rib cage, tenderness may be elicited by fist percussion or deep pressure between the ribs. In central abscesses of the right lobe, the patient often complains of pain in the right loin. This pain was so persistent and intense in one of our cases that aspiration was attempted because a perinephritic collection was suspected. Abscesses presenting anteriorly produce tenderness below the costal margin, and in well-advanced cases a definite bulge may often be noted just below the costal margin.

In deciding upon treatment of amebic hepatic abscess, there seems to be little controversy in the literature (3, 5). That amebic hepatitis and uncompli-

cated abscess should be treated by systemic emetine seems well-accepted. If the looked-for improvement does not occur after one such course, aspiration of the abscess is recommended. Although stress is laid on the fact that the aspirating needle should not traverse a serous cavity, it is difficult to see how a liver abscess may be aspirated without traversing at least the peritoneal cavity. In our experience, there is no "walling off" of the peritoneal cavity by adhesions between the serous covering of the liver and the parietal peritoneum, even in abscesses with secondary infection. Of course, "walling off" occurs when rupture takes place, but drainage should be performed before this occurs. We have seen no extension of the amebic or infective process from aspiration or drainage if emetine and penicillin are used in the postoperative period.

SURGICAL TREATMENT

The aspirating needle may be introduced below the rib margin anteriorly or laterally. The procedure should be carried out in the operating room where complications may be cared for if they arise. A large needle must be used. As much "pus" as possible should be removed and the needle withdrawn. The literature suggests a lower mortality by closed aspiration than by open drainage (3, 4).

There also seems to be agreement that in cases of infected amebic hepatic abscess, open drainage should be performed after at least four days of emetine treatment. It is apparent from our experience as well as others (4) that infected abscesses do not respond to emetine therapy or even emetine combined with penicillin, and carbarsone and they may even go on to perforation during this treatment. This is no criticism of the treatment and it is recommended, but operation should not be delayed because of it if the diagnosis has been made. The diagnosis of secondary infection is presumptive if there is a history of high fever, chills and high leucocytosis.

In two of our cases, liver abscess was unsuspected until encountered at operation. In both of these, the abscess presented on the under surface of the liver, and the operation was performed with a diagnosis of acute gallbladder disease in one patient and infected pancreatic cyst in the other. Drainage was performed without preoperative emetine and the result was excellent in both cases.

The technic of drainage of a liver abscess varies with the location of the abscess. For those in the lateral portion and dome of the right lobe we prefer a two-stage transdiaphragmatic procedure. The abscess is located by exploring with an aspirating needle under local anesthesia at the site of the most acute local tenderness produced by fist percussion or deep intercostal pressure. A large, long needle should be used. When pus is found, a small amount is

aspirated, enough to relieve tension in the abscess, and to serve for smear and bacteriologic study. The needle is detached from the syringe and left in place, and the rib above or below the needle is resected subperiosteally for a distance of about 2 inches. Care should be taken not to injure the underlying pleura. The wound thus produced is tightly packed with iodoform gauze, the aspiration needle is then removed and a tight dressing applied. After an interval of three or four days, the patient is returned to the operating room, and under local anesthesia, the iodoform packing is removed. The parietal and diaphragmatic pleura is now adherent, and transdiaphragmatic drainage may be carried out without danger of infecting the pleural cavity. The exploring needle is again used to locate the abscess cavity and, with this as a guide, the abscess is opened through the diaphragm. Once pus is located, an aspirator is used to evacuate the contents of the cavity and the opening is enlarged sufficient to permit the introduction of one or two large rubber drainage tubes. An iodoform pack is used to control the ooze by introducing it along the tubes into the abscess cavity and in the wound.

For anterior abscesses, it is safer to make a small incision over the area of greatest tenderness and to explore with an aspirating needle under direct vision. When the abscess has been located, the needle is left in place and the abdomen walled off with iodoform gauze between the surface of the liver and the parietal peritoneum, leaving a space an inch or more in diameter around the needle. With the needle as a guide, an electrocautery is used to enter the abscess. The pus is evacuated by rapid aspiration, and drainage and packing are introduced as described above.

Because most of our cases were secondarily infected, penicillin was given in adequate dosage, and emetine was continued for a total of ten days, or was begun if it had not been used preoperatively. The packing was removed on the fifth day. By this time, the fever usually had dropped to normal, and the anorexia and malaise had disappeared. Care must be exercised when the packing is removed, especially in large centrally-located abscesses in the right lobe, lest secondary hemorrhage be started. The abscess cavity is seen to be lined with grayish necrosis, which rapidly disappears if irrigations of 1:1,000 emetine solutions are used daily or every other day. In one patient in whom saline irrigations were employed, no improvement was noted until emetine solutions were used instead of saline. (Electrocardiograms were used to check the effect of the emetine irrigations on the myocardium but no change was noted.)

We were never able to demonstrate ameba from the pus or abscess scrapings in any of our cases, but the dramatic response to emetine left no doubt as to the amebic origin of the abscesses.

The pus obtained on evacuation of the secondarily infected abscess is usually the thick creamy pus of a pyogenic infection rather than the typical "chocolate-

sauce" pus characteristically found with amebic abscess. Colon bacilli and streptococci are the most common infecting organisms.

The recurrence of symptoms after drainage of an abscess usually is due to the appearance of a second abscess. This may be adjacent to the first and eventually rupture and drain through the original abscess cavity, or it may be some distance away and require a second incision and drainage. In our experience, a second abscess may form and give symptoms in spite of or during emetine and penicillin therapy.

Case 1. J. R. K., a 20-year old white B.M.2/c, was admitted to the hospital 10/24/44 with a diagnosis of duodenal ulcer for observation. In September, while aboard ship returning from North Africa where he had made liberty in several ports, he developed a severe attack of diarrhea and fever which lasted one week. There was no medical officer aboard, and his treatment consisted only of bed rest. He lost 15 pounds during this illness. When he arrived in the United States his diarrhea had stopped and he felt well although weakened. He went on leave, and although he failed to regain his weight and strength, he had no particular complaints. About 20 days before admission, he developed malaise and loss of appetite and observed pain in his right upper abdomen which occasionally radiated posteriorly. These symptoms became progressively more severe, and fever and chills developed. On admission, he appeared acutely ill, with a temperature of 102°F., pulse 120 and W.B.C. 30,000. An x-ray film of the chest was negative. Because of his acute upper right abdominal pain and tenderness, the patient was operated upon with a diagnosis of acute gallbladder disease or ruptured peptic ulcer, but no gallbladder or other disease could be demonstrated. Although the liver was inspected, nothing was noted to warrant an exploration by aspiration, and the abdomen was closed. The patient was given intensive penicillin therapy, and needle exploration of the lumbar area was done because a perinephritic collection was suspected. His condition became worse, and he developed a slight jaundice and slight ankle edema. His liver became enlarged, and he developed pain in the right chest and shoulder on inspiration. His W.B.C. ranged from 13,000 to 30,000 and his temperature elevated daily to 102°F. to 104°F. A chest film revealed an enlarged liver with elevation of the diaphragm. In the comparatively short period of severe illness he had lost about 60 pounds.

The patient's condition was critical when, on 11/4/44, he was operated upon through a right upper abdominal incision. A single large abscess containing 1000 cc. of thick, yellow pus was located in the right lobe of the liver. Drainage was instituted as an emergency procedure through a double-barreled large rubber tube and the wound and the abscess cavity packed with iodoform gauze. No ameba were demonstrated, and there was no growth on culture from the abscess fluid.

The postoperative course was very stormy because the patient was in such an extremely toxic state and because his recovery was complicated by a series of severe hemorrhages from the huge abscess cavity (fig. 1). At one point, his weight was down to 82 pounds whereas his normal weight was 176. The gravity of this patient's

condition is witnessed by the fact that during his illness he was given over 7000 cc. of whole blood and 2000 cc. of plasma. He received two courses of emetine hydrochloride, one grain intramuscularly daily, and carbarsone, $3\frac{3}{4}$ grains daily for ten days. Not until the abscess cavity was irrigated with emetine, 1:2,500 twice daily, did it begin to close. When receiving the emetine by both routes he appeared to do much better clinically. He gradually improved, and there was a final cessation of drainage from the abscess on 5/19/45. At this time, he weighed 145 pounds.

Case 2. W.T., a 37-year old white boatswain, was admitted to the hospital 12/31/44 with a diagnosis of hydronephrosis which had been discovered on a routine, annual physical examination in North Africa where he had been on duty for twenty

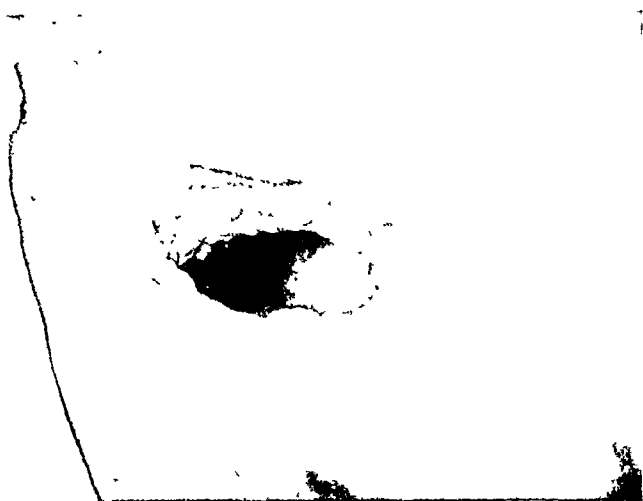


FIG. 1. CASE 1. VIEW OF THE RIGHT UPPER ABDOMEN, SHOWING THE LARGE CAVITY IN THE RIGHT LOBE OF THE LIVER FOLLOWING DRAINAGE

Healing did not begin to occur until the abscess was irrigated with emetine 1:2,500. (Official U. S. Naval Photograph)

months. He had been well except for two bouts of severe, prolonged diarrhea, the last attack in November, 1944. He continued his duty during these illnesses, and did not report to the hospital for treatment. Because of the hydronephrosis, he was transferred to the United States for treatment and disposition.

On 1/4/45, after a genito-urinary work-up, a left nephrectomy was performed. His recovery was complicated by a low-grade wound infection and a minimal left bronchopneumonia, which cleared rapidly with penicillin therapy. On March 3, two consecutive stools were positive for *Endamoeba histolytica* so a course of emetine, 1 grain daily, and carbarsone, $3\frac{3}{4}$ grains twice daily, for ten days was instituted. A few weeks later while he was still in the hospital, he began to complain of dull pain in the right upper quadrant and loss of appetite. Gallbladder disease was suspected, and he was studied and treated with that in mind. No gall stones were

demonstrated, but a gallbladder series, including an intravenous administration completed on 4/15/45, showed a failure of the gallbladder to visualize. His symptoms persisted and became worse. He developed some pain in the lower right chest, which occasionally radiated to the right scapula. During this time he lost 30 pounds of weight. He had developed a slight daily elevation of temperature to 99°F. to 101°F., and a leucocytosis ranging between 14,000 and 20,000. His R.B.C. ranged from 4,300,000 to 4,700,000.

On 5/12/45, roentgenographic examination revealed an elevated right diaphragm, and a final pre-operative diagnosis of liver abscess was made. On 5/15/45, operation was performed. An aspirating needle was inserted at the point of maximum tenderness, which was in the eighth interspace at the anterior axillary line. The abscess was located, and thick yellowish fluid was aspirated. Under local anesthesia, 2 inches of the ninth rib were resected. The wound was then packed with strips of iodoform gauze. The second stage of the operation was performed three days later, when the abscess was opened at this point and 300 cc. of thick yellow fluid was evacuated. A rubber drain was inserted and the cavity packed with iodoform gauze. No ameba were demonstrated in the fluid nor were any other organisms found on direct smear. Culture demonstrated gram positive streptococci.

The immediate postoperative course was excellent. The patient's temperature and pulse returned to normal in two days and he felt better generally. He received emetine hydrochloride, one grain daily, and irrigations of the abscess cavity with 1:2,500 emetine solution twice daily. However, on the 12th postoperative day, he began to develop a right pleural effusion. On 6/4/45, 640 cc. of slightly turbid fluid were removed. No organisms were demonstrated on smear or culture. His condition improved and his temperature and pulse returned to normal. One week later, he began to develop pain in the epigastrium and right chest. Again the temperature rose to 100°F. to 101°F. and the pulse to 120. X-ray showed the diaphragm to be elevated. On 6/14/45, operation was performed through a transverse upper abdominal incision. A second liver abscess the size of an orange was found on the anterior surface of the liver in the right lobe. The abdominal cavity was packed off and the abscess was drained, a large rubber tube was inserted into the abscess and it was packed with iodoform gauze. The temperature and pulse returned to normal the following day. He received another course of emetine hydrochloride, one grain daily for ten days, and the abscess was irrigated twice daily with emetine hydrochloride, 1:2,500. He continued to make gradual improvement, and on 7/18/45 his wounds were healed and he was permitted to go on sick leave.

Case 3. W. E. C., a 24-year old white S 1/c, had been on duty in North Africa for two months when, in December, 1944, he suffered a severe attack of diarrhea with many bloody stools. He was ill for about two weeks, and several stools were examined for parasites but none was demonstrated. His diagnosis was reported as colitis, and when his diarrhea was arrested he was discharged to duty. On 3/1/45, he developed some fever and malaise and was admitted to the hospital with a diagnosis of catarrhal fever. He was discharged after 22 days, but stated that he continued to feel poor generally. He developed pain in his right side and on 4/13/45,

an appendectomy was performed. The patient stated that the pain was high up on his right side, and that it was still there following the operation and later became worse. He had a stormy convalescence, continuing to lose weight, becoming anemic with a R.B.C. of 3,200,000 and requiring several whole blood transfusions. He continued to run an intermittent temperature of 99°F. to 101°F.



FIG 2. CASE 3. LATERAL VIEW OF THE CHEST TO SHOW MARKED ELEVATION OF THE DIAPHRAGM IN A PATIENT WITH AN ABSCESS OF THE RIGHT DOME OF THE LIVER

(Official U. S. Naval Photograph)

He was evacuated to the United States for treatment, arriving at the hospital 5/11/45. He had lost 37 pounds, had pain and tenderness in right upper quadrant and lateral chest wall in the region of the eighth and ninth ribs. His liver was palpable three fingers below the costal margin. W.B.C. varied between 11,000 and 24,000, and a chest film demonstrated the right diaphragm to be elevated (fig. 2). A final preoperative diagnosis of liver abscess was made, and on 5/18/45, operation was performed. Aspirations attempted through the eighth and ninth interspaces failed to draw any fluid so an upper abdominal incision was made and the liver explored.

An abscess was palpated in the right lobe, and there were many small adhesions between the superior surface of the liver and the diaphragm. The point at which the abscess was located was marked, the abdominal incision closed and the abscess aspirated through the eighth interspace. Thick, dark bloody fluid was found. A section of the ninth rib was resected, and iodoform gauze packed in the wound. Three days later the second stage was performed. The abscess was entered through the previously prepared wound and opened with cautery. A large single abscess was found with 250 cc. of dark, thick, "chocolate-sauce" type of drainage. A large rubber drain was inserted, and the abscess and wound packed with iodoform gauze



FIG. 3. CASE 3. ANTEROPOSTERIOR VIEW SHOWING ELEVATION OF THE DIAPHRAGM AND THE ABSCESS OUTLINED WITH IODOFORM PACKING TO SHOW ITS SIZE AND POSITION

(Official U. S. Naval Photograph.)

(fig. 3). No organisms were demonstrable in the fluid. Since there was a history strongly suggestive of amebiasis and since the single abscess in the right lobe of the liver was typical of amebic liver abscess, the patient was put on a course of emetine hydrochloride, one grain daily for ten days. The abscess cavity was irrigated twice daily with emetine hydrochloride, 1:1,000. Convalescence was very smooth. Temperature and pulse decreased promptly, and there was a gradual gain in appetite, strength and weight. One month postoperative the abscess cavity was obliterated, the wound in the chest wall practically healed and the patient had gained 14 pounds in weight.

Case 4. J. P., a 50-year old veteran, had been discharged from the army after

a year of duty as sergeant in the South Pacific. He had had an attack of diarrhea in New Caledonia. One stool examination was "suggestive" of ameba, but other repeated examinations were negative. He was in the Philippines when the war ended, and had had no symptoms except an occasional attack of diarrhea lasting a day or two. For two months prior to admission he had not been well. Anorexia, malaise, a weight loss of 31 pounds, and intermittent fever of 99°F. to 102°F. were



FIG. 4. CASE 4. ABSCESS OF UNDER SURFACE OF THE LEFT LOBE OF THE LIVER, SHOWING DISPLACEMENT OF THE STOMACH TO THE LEFT

(Official U. S. Naval Photograph.)

his chief symptoms. About 9/4/45, he developed acute pain in the upper left abdomen.

Physical examination showed evident weight-loss and slight icterus. There was marked tenderness over a grapefruit sized mass in the epigastrium and left upper quadrant. He had slight pain on deep inspiration. An x-ray examination showed a large mass displacing the stomach to the left (fig. 4). Leucocytosis ranged from 13,000 to 20,000. A tentative diagnosis of infected retroperitoneal tumor or infected pancreatic cyst was made.

On 9/15/45, an abdominal exploration was made through a midline upper abdomi-

nal incision. The mass was found to lie in the left lobe of the liver. Aspiration obtained thick yellow pus. After packing of the abdomen, the abscess was opened with a cautery and about 600 cc. of pus evacuated. Drainage with large rubber tubes and iodoform gauze was instituted. The pus showed *B. coli* and anerobic streptococcus. Postoperative care with penicillin and emetine irrigations, 1:1,000 solution twice daily, resulted in rapid healing. The tubes were gradually shortened and were entirely removed on the 21st postoperative day. Seven weeks after operation, the patient was discharged with his wound healed and a gain in weight of 20 pounds.

SUMMARY

Hepatic abscess of amebic origin should be encountered with increasing frequency in service personnel who have had duty in areas where amebiasis is endemic. The diagnosis is not always easy because the demonstration of ameba in the stools may be difficult, the history indefinite, and the period from dysentery to abscess considerably long. The symptoms and signs of the simple and secondarily-infected abscess are outlined.

Emetine and aspiration may be tried, in the order named, in noninfected abscesses. Drainage is indicated for abscesses which are secondarily infected. The type of drainage preferred is given. Drainage should be preceded by or combined with emetine and penicillin therapy. Four case reports are included which illustrate the difficulties of diagnosis in these cases.

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OBSERVATIONS ON FIVE HUNDRED AND FORTY-THREE CASES OF PEPTIC ULCER

FREDERICK F. RADLOFF, M.D.

Seattle, Washington

INTRODUCTION

This series comprises observations on 543 cases of peptic ulcer during the period from September, 1942 to September, 1945. The information was collected from patients seen on the gastrointestinal section of a large Army general hospital in Hawaii and represents 14.7 per cent of 3675 admissions to the gastrointestinal section of this hospital. An opportunity to study the ulcer patient before and after combat was obtained. Many racial types from the local inductees of Hawaiian, Chinese, Filipino, Portuguese, and Japanese descent were seen. Many developed their symptoms prior to sailing to Guadalcanal, Samoa, The Gilbert Islands, The Marshall Islands, Saipan, Guam, and the Philippine Islands. Others had returned from these areas via ship or plane, for medical reasons. Thus the soldier who developed gastrointestinal symptoms prior to combat could be contrasted with the one who had developed symptoms afterwards. An excellent opportunity to compare the ulcer patient and the psychoneurotic under these extreme conditions was afforded.

INCIDENCE

The age incidence varied from 18-51 years, the average being 31. Duodenal ulcers accounted for 95.6 of the total. Complications were rare. There were 48 with massive gastrointestinal hemorrhage. Only those whose red blood count fell below 3.5 million or hematocrit below 3.5 were counted in this group. Thirty-seven were seen with acute perforation and 4 with obstruction. The low incidence of gastric ulcers and complications is accounted for on the basis of the younger age group in the military service. Sixty per cent of the massive gastric hemorrhages and 45 per cent of the perforations occurred without any antecedent history of pain. Only one patient with complications was over 45 years.

Racial incidence included 17 negroes, 10 Hawaiians, 7 American Indians, 3 Filipinos, 1 Chinese, and no Japanese. It is notable that 60 per cent of all soldiers of Hawaiian descent with abdominal symptoms proved to have peptic ulcers and that 60 per cent of them were gastric.

ETIOLOGY

The cause of peptic ulcer has never been determined. It is generally agreed that the stomach of a patient with peptic ulcer has lost its ability to resist the

digestive action of the acid pepsin secretion. It is well established that the presence of free hydrochloric acid is necessary for ulcer production. Much experimental work has been done recently to prove the importance of the pepsin inhibiting factor of certain alkalies. Sandweiss (1) has demonstrated the importance of continuous nocturnal secretion in keeping an ulcer active; also that nocturnal gastric acidity is no higher in ulcer than in non-ulcer patients.

During the war the psychosomatic element in production of ulcer has been emphasized. In the military service the environment is fixed and can not be readily altered except by dismissal from the service. In civilian life changes in environmental influences are easier. Dragstedt (2) and others have sectioned the vagus nerves to control the cephalic phase of gastric motility and secretion. Ivy (3) has used enterogastrome, an extract of intestinal mucosa, to prevent ulcer in Mann Williamson dogs, and Sandweiss (4) has used urogastrone, a urinary extract to prevent ulcer experimentally. This work shows that advances are being made in controlling the hormonal and psychic factors involved in production of peptic ulcer.

Wolf and Wolff (5) were able to observe the effects of the psychogenic factor in their patient with a gastrostomy. They observed the mucosa directly under varying states of emotional tension, and showed that resentment, hostility, anxiety, and aggressiveness caused changes in the gastric mucosa. Obviously the soldier is subjected to this psychic state frequently. It is easy to see how digestive symptoms can occur under such conditions but it is difficult to see why only a small percentage develop peptic ulcer and why the average psychoneurotic has many abdominal symptoms but does not develop ulcer.

DIAGNOSIS

Differential diagnosis was primarily between peptic ulcer and functional digestive disturbances without demonstrable organic disease. This differentiation could be made on the basis of history, physical examination, laboratory, x-ray examination, and response to therapy. This series does not include any case not confirmed by x-ray or fluoroscopic examination. We were aware that an occasional case of peptic ulcer occurred without demonstration by x-ray, but because of the acute man power shortage in the Pacific theater we felt justified in treating those with typical symptoms vigorously for a few weeks and returning them for a trial at duty.

The history varied as to age, duration, and associated psychosomatic symptoms. Food relief or periodicity was present in 92 per cent of the patients. Occasionally in cases of long duration the periodicity was lost. Those with ulcer were definite about the time of onset of symptoms and described accurately the type of pain experienced. It was gnawing, aching, or cramp-like in character. Pain before breakfast was not common; usually it occurred

before the noon or evening meal, or awakened the man at night. Radiation through to the lower thoracic or upper lumbar area was rarely noted in the absence of underlying organic disease.

Vomiting was rare in those with ulcer and almost universally present in the psychoneurotics with digestive complaints. Soda relief was of no diagnostic aid, since most patients with functional digestive disorders admitted relief from soda. Sour eructations, pyrosis, and aggravation by food did not favor the diagnosis of ulcer.

Physical examination showed the ulcer patient to conform to the usual asthenic type so commonly described. However, several with athletic and obese physical characteristics were seen. These were usually seen in those with acute onset of symptoms, sudden massive hemorrhage or perforation in the absence of previous abdominal symptoms. The only constant physical finding was localized tenderness in the mid-epigastrium.

Complete blood studies, including red blood counts, hemoglobin estimation, white blood counts and differential counts were done on all patients. Urine analysis, gastric analysis, and stool examinations for ova, parasites and blood were done routinely. No proven case of ulcer had a total achlorhydria after histamine injection. There was a remarkable tendency toward hypoacidity. Thirty-three per cent had a free hydrochloric acid of less than 25 units, and 25 per cent had an acidity greater than 50 units. A large majority with active symptoms had a positive occult blood reaction in the stool. Co-existing parasitic infestations were found in 27; 15 had hookworm, 7 *Strongyloides*, 5 *trichuris*, and 3 tapeworm.

TREATMENT

The more simple methods of treatment were usually sufficient, since the patients were young with few complications and a short history. Frequent small feedings at two to three hour intervals with one nightly feeding was usually sufficient. This was supplemented by antispasmodics, sedation, and alkalis in the form of aluminum hydroxide. The average patient experienced complete symptomatic relief in seven to ten days on this regime. Only in the rare case with an ingrained psychoneurosis was there an unfavorable response to treatment. A favorable response to therapy was almost diagnostic of ulcer. Psychoneurotics with digestive complaints seldom received more than temporary partial relief from the same therapy.

Treatment of complications was more difficult. Gastrointestinal hemorrhage was treated by medical management. Surgical interference was not necessary although many were admitted in shock. This was possible because of the low age incidence, only one being over 45. Blackford (6) has shown that mortality is high in those above 45, and only one of this series fell in that group.

If shock was present transfusions of whole blood or plasma were given. This

group tolerated large amounts of whole blood without any apparent ill effects. Feeding was started early, as soon as nausea subsided. Frequent feedings of milk and cream were given. The more bulky Meulengracht diet was not used. It appeared to cause nausea and at times vomiting. Sedation in the form of dilaudid and phenobarbital was used.

After recovery from the acute effects of the hemorrhage more liberal feedings of high protein diet were given. Strict bed rest for a minimum of twenty-one days was instituted, after which fluoroscopy was done. There were no deaths in this group.

DISCUSSION

Of particular interest in this group is the contrast between the ulcer patient and the psychoneurotic with digestive symptoms. The psychic make-up of this group of ulcer patients was in direct contrast to that of the psychoneurotic. Vague associated symptoms referable to systems other than the gastrointestinal tract were rare in those with ulcer. The average ulcer patient gave a definite clear cut history. He knew exactly when his pain began and how frequently it occurred. He localized it in the epigastrium. He denied nervousness and did not volunteer other vague symptoms such as lack of appetite, weakness, dizziness, headache, palpitation, or vomiting; commonly he was a non-commissioned officer with a good work record. He appeared energetic and aggressive. There was an obvious underlying tension, an attitude of frustration. Outwardly he was relaxed but inwardly he was tense. This tension was brought on by trying too hard and by overconscientiousness. His facial expression was apathetic and often he appeared unconcerned about his symptoms.

This was in direct contrast to the psychoneurotic, who gave a poorly correlated history with many associated vague symptoms. He appeared tense, apprehensive, outwardly nervous and afraid. He expressed deep concern over his symptoms. Usually his past history showed development of psychosomatic complaints under pressure. There was seldom any periodicity to his story. He subconsciously hoped that some organic disease would be found to account for his inadequacy. This type of individual rarely proved to have an ulcer.

It was also interesting to note that 47 per cent of this series had a history of abdominal pain prior to entry into the service, many dating back to age nine to age twelve. In our series the periodicity was frequently present in the teen age but was often lost after several years of recurrent symptoms. Many, however, had been symptom free for years before entry into the service. The predisposing factor had been present for years and the military service had merely aggravated a preexisting ulcer diathesis.

SUMMARY

(1) Five hundred and forty-three cases of peptic ulcer taken from 3695 admissions to the gastrointestinal section of a large Army general hospital in Hawaii are reported.

(2) In general the typical history of dull, aching, epigastric pain between meals with relief by food was present.

(3) The psychoneurotic seldom developed peptic ulcer and rarely gave a history suggestive of ulcer.

(4) Approximately 10 per cent of the complications occurred without previous abdominal pain. This group was commonly the athletic or obese type.

(5) Medical management produced complete symptomatic relief in seven to ten days.

(6) Massive gastrointestinal hemorrhage responded well to medical treatment and no fatalities were recorded.

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A STUDY OF THE GASTRIC SECRETORY RESPONSE IN THE AGED*

HENRY A. RATSKY, M.D. AND MICHAEL WEINGARTEN, M.D.

From the Hospital and Home of the Daughters of Jacob, New York, N. Y.

Forty years ago Bidder and Schmidt, and others (1) demonstrated that the quantity of the digestive juices diminished with age. In 1932, Vanzant, Alvarez, Eusterman, Dunn and Berkson (2) showed by means of a single extraction after a test meal that the incidence of achlorhydria in normal people increased from youth to old age. Bloomfield, (3) utilizing the fractional test meal, and Polland, (4) the histamine test, corroborated this observation, but the latter found a lesser percentage of achlorhydria in the various age groups after histamine stimulation. In none of the above studies were attempts made to ascertain whether the achlorhydrias, especially in the advanced age group, were true achylas, namely, an anacidity refractory to histamine with an absence of gastric ferments. Furthermore, so much emphasis has been placed on the comparatively large incidence of achlorhydria in individuals past sixty, that scant attention has been paid to the presence of hyperchlorhydria in the aged. Sagal, Marks and Kantor (5) thought that high acid values in old age might be considered an index to longevity. Clinically, it is not an uncommon experience to see a patient of advanced age who suffers from a peptic ulcer. At times the first symptoms of this disease may appear in an aged individual. It was therefore thought of interest to make a study of the gastric secretory response in a group of apparently normal persons sixty-five years of age and over.

This study is based on a series of forty-seven normal persons who were ambulatory, and who had no gastrointestinal complaints except the usual degree of constipation found in old people. Their ages ranged between sixty-five and eighty-five years. Three of the individuals were between sixty-five and sixty-nine years of age; thirty-three were between seventy and seventy-nine years, and eleven between eighty and eighty-five years. Sixteen of the subjects were males and thirty-one were females.

METHOD

The gastric secretion of each individual was determined as follows:—A test meal of two slices of toast and one glass of water was given and fractional determinations made every fifteen minutes. While an attempt was made

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to carry out the examination for an hour, this was not always possible in many of the aged subjects. In those persons in whom no free hydrochloric acid was found, histamine hydrochloride was administered in a dosage of 0.1 mg. to each ten kilograms of body weight. These fractional determinations, after histamine, were made for sixty minutes. In all of the cases in which achlorhydria was found the gastric contents were examined for ferments. The proteolytic activity was tested by the use of Mett tubes, and the milk-coagulating activity by the standard procedure. The absence or presence of lactic acid was also noted.

RESULTS

In twelve subjects no hydrochloric acid was found with the bread and water fractional meal, but when histamine was administered, only eight, or 17 per cent of the forty-seven persons, proved to be cases of true achlorhydria (table

TABLE 1

UNITS FREE HCl	AGE GROUPS						NUMBER OF PATIENTS	PERCENTAGE
	65-69		70-79		80-85			
	M	F	M	F	M	F		
False Achlorhydria.....				3		1	4	8.5%
True Achlorhydria.....	1			6		1	8	17.0%
2-19 Units.....			2	5	1	5	13	27.7%
20-34 Units.....		1	3	1			5	10.6%
35-50 Units.....		1	3	4	1	2	11	23.5%
51 or more Units.....			5	1			6	12.7%

1). In none of these eight cases was there a true achylia. Milk was coagulated in all of the specimens in the subjects with achlorhydria. Proteolytic activity was present in the fasting specimens of all but two subjects with histamine achlorhydria, but it did appear following the injection of histamine in one case; while in the other no proteolytic activity followed the injection of histamine (table 2). Lactic acid was found in six of the cases of true achlorhydria and was absent in one of them. In one case it was not examined. In thirteen of the forty-seven individuals (27.7 per cent), the range of free hydrochloric acid with a bread and water test meal, was from 2 to 19 units; in five persons (10.6 per cent), it was 20 to 24 units; and in eleven persons (23.5 per cent), it was between 25 to 29 units. In six individuals (12.7 per cent), the free hydrochloric acid was in excess of 50 units (table 3). Two of these six subjects with hyperchlorhydria had an acidity above 50 units but not exceeding 59 units;

two ranged between 60 and 84 units of acid; and two between 85 and 99 units of free hydrochloric acid.

TABLE 2

NAME	SEX	AGE	TEST MEAL	SPECIMEN	FREE HCl	TOTAL ACID	MILK CO-AGULATION	PROTEOLYSIS	LACTIC ACID
R. K.	F	73	*B&W	fasting	0	7			
				15 min.	0	8			
				30 min.	0	5			
				45 min.	0	7.5			
			Hist.	fasting	0	7.5	pos.	neg.	ft. tr.
				15 min.	0	10	pos.	QNS	QNS
				30 min.	0	7.5	pos.	QNS	QNS
				45 min.	0	10	pos.	1+	ft. tr.
				60 min.	0	15	pos.	neg.	ft. tr.
F. K.	F	70	*B&W	fasting	0	7			
				15 min.	0	5			
				30 min.	0	5			
				45 min.	0	9			
			Hist.	fasting	0	17.5	pos.	neg.	ft. tr.
				15 min.	0	17.5	pos.	neg.	ft. tr.
				30 min.	0	15	pos.	neg.	ft. tr.
				45 min.	0	12.5	pos.	neg.	ft. tr.
				60 min.	0	12.5	pos.	neg.	ft. tr.

* 2 slices bread and a glass of water.

TABLE 3

Hyperacidity in aged

GRADE (BOCKUS)	SEX	AGE	TEST MEAL	MAX. FREE HCl	MAX. TOTAL ACIDITY
I (50-59 Units)	M	70	*B&W	52	71
	M	78	B&W	52	82
II (60-84 Units)	M	78	B&W	68	96
	M	78	B&W	73	87
III (85-99 Units)	M	79	B&W	85	102
	M	78	B&W	98	108

* 2 slices bread and a glass of water.

COMMENT

In a study of the gastric secretory response in a group of forty-seven apparently normal aged individuals, free hydrochloric acid was 19 units or less in twenty-five, or 53.2 per cent, of the subjects. While this confirms the fact

that there is a tendency to a diminished acidity in the normal aged, the number of subjects (17 per cent) in whom a true achlorhydria was present, was less than that found in other studies. Furthermore, in none of these forty-seven persons was there a true achylia with absence of all ferments. In one, proteolytic activity was absent, but milk-coagulating activity was present. This raises the question as to whether the adult human gastric juice contains both rennin and pepsin. There is a difference of opinion on this subject. Several authors (6) mention the presence of rennin in the gastric juice. Dotti and Kleiner (7) presented evidence that rennin was absent from adult human gastric juice. Cowgill (8) stated that pepsin, itself, coagulates milk. In this study, the fasting specimen, as well as the specimens following histamine, coagulated milk in every case of true achlorhydria. As previously mentioned, proteolytic activity was absent in the fasting specimen in two persons with histamine achlorhydria, but appeared following the injection of histamine in one case, while in the other, no proteolytic activity followed the injection of histamine. This disassociation between milk-coagulating and proteolytic activity, if found in any considerable number of achlorhydric stomachs, would on the surface, seem to indicate the presence of two separate enzymes. However, it may very well be that the hydrogen ion concentration of a given gastric juice may be such as to permit milk-coagulation but not proteolysis by the same enzyme, pepsin.

Another interesting aspect of the results of this investigation of gastric secretion in the aged, and one which is not usually emphasized, is the fact that hyperchlorhydria was found in six or 12.7 per cent of the subjects. These findings are of especial interest, in view of the fact that in a previous paper (9) we pointed out that 56, or 13.7 per cent, of 408 cases of bleeding peptic ulcer were in patients between the ages of sixty to eighty-six years. One of the severest cases of bleeding encountered in that series, was in an individual whose first symptom of a pyloric ulcer was a gastric hemorrhage which occurred during his seventy-sixth year. Therefore, it seems worthy of note that hyperchlorhydria in the normal aged is not an uncommon finding, though it does not occur as frequently as diminished acidity or true achlorhydria.

SUMMARY

1. 53.2 per cent of a group of forty-seven apparently normal persons above 65 years of age had 19 units or less of free hydrochloric acid after a bread and water test meal.
2. 17 per cent of this group were found to have true achlorhydrias.
3. 12.7 per cent had a hyperchlorhydria.
4. No case of complete achylia gastrica was found.
5. Milk-coagulating activity was present in every case of histamine achlorhydria; in two achlorhydric persons who showed no proteolytic activity in the

fasting specimen, one did, and one did not show this activity after histamine stimulation.

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APPARENT LACK OF RELATIONSHIP BETWEEN LEVELS OF B-VITAMINS IN THE FECES AND DIETARY SUPPLEMENTATION WITH CRYSTALLINE B-VITAMINS AND PROTEIN

MYER FREED, PH.D., WALTON E. GRUNDY, M.S., CHARLES R. HENDERSON, M.S. AND
GEORGE H. BERRYMAN, M.S., PH.D.

From Army Medical Nutrition Laboratory, 1849 West Pershing Road, Chicago, Illinois, an installation under the jurisdiction of the Surgeon General, U. S. Army

WITH

THEODORE E. FRIEDEMANN

From Laboratory of the Abbott Fund, Passavant Memorial Hospital, Chicago, Illinois

INTRODUCTION

Several reports in the literature have dealt with the relationship of the character of the diet to the levels of vitamins excreted in the feces. In particular, the types of carbohydrate used, such as sucrose, lactose, dextrin, and corn starch, appear to have varying influence upon the symbiotic production of vitamins in the intestinal tract of animals (1), (2), (3), (4).

In the course of investigation of effects associated with decreased intakes of B-vitamins and animal protein by seven normal volunteer young men, crystalline supplements of the B-vitamins and protein were given orally and additively during successive periods of the experiment. Frequent determinations of the levels of B-complex vitamins in the feces were made.

The purpose of this report is to describe the trends of the fecal vitamin levels during the period of supplementation.

EXPERIMENTAL

Subjects. The subjects were seven volunteers, 23 to 28 years old, judged to be free from significant organic disease or defects. These men were housed under identical conditions in a hotel, and later a student dormitory. All ate the same diet, which remained unchanged during the entire experimental period. The principal testing activity was provided by standardized daily tasks in the chemical laboratory or in school. The remaining free time was spent by participating in various sports, clerical and scholastic work, outdoor walks, etc.

Diet. All meals were prepared and served under the direct supervision of a trained dietitian. The menu was followed strictly, and all portions were carefully weighed. Extra identical meals were prepared one day each week, carefully ground, homogenized, frozen and used for assay. The canned foods were purchased in one lot of the same pack in a quantity sufficient for

the entire experiment. During an initial control period of 12 weeks a normal diet supplying liberal quantities of all nutrients was fed to all 7 subjects. The content of this diet in the B-vitamins under consideration is shown in table 1. Thereafter an experimental diet was fed, providing daily about 3300 calories, 40 grams of protein, 380 grams of carbohydrate, 175 grams of fat, 200 mg. of calcium, 560 mg. of phosphorus, 12 mg. of iron, 90 mg. of ascorbic acid and 16,000 I. U. of vitamin A. Approximately 27% of the entire caloric intake was provided in the form of corn meal or other corn products. The determined (by analysis) average daily food content of the B-vitamins under consideration in this report is also listed in table 1. These values represent

TABLE 1
Nutritional content of the normal and experimental diets

NUTRIENTS		NORMAL DIET	EXPERIMENTAL DIET
Calories.....		3170*	3300*
Protein.....	gm.	70*	40 (a)
(1-Tryptophane).....	mg.	700-900	210-300
Calcium.....	gm.	.86*	.20*
Phosphorus.....	gm.	1.26*	.58*
Iron.....	mg.	15.5*	12.00*
Thiamine.....	mg.	1.44	.50
Riboflavin.....	mg.	1.84	.30
Niacin.....	mg.	15.6	5.8
Biotin.....	mcg.	44	19.0
L-casei Factor.....	mcg.	64	23.0
Pantothenic Acid.....	mg.	4.7	1.1
Pyridoxine.....	mg.	1.76	1.1
Ascorbic Acid.....	mg.	105*	90*
Vitamin A.....	I.U.	7400*	16600*

* Calculated.

FIG. 1. EXCRETION OF B-VITAMINS IN FECES

The vertical lines numbered 1 to 7 designate the time at which different supplements were added:

- (1) Start of experimental diet.
- (2) Calcium caseinate, thiamine, riboflavin, nicotinamide and the lesser known B-vitamins added to the diet of the control subject in quantities described on page 3.
- (3) 1.2 mg. per day of thiamine added to the diet of experimental subject.
- (4) Two separate 25 mg. doses of thiamine hydrochloride administered intravenously to both control and experimental subjects.
45 gm. per day of calcium caseinate added to the diet of the experimental subject.
10 mg. riboflavin and 200 mg. nicotinamide administered intravenously to the experimental subject.
1.5 mg. riboflavin and 12 mg. nicotinamide per day added to the diet of the experimental subject.
- (5) Crystalline lesser known B-vitamins added to the diet of the experimental subject.
- (6) Both experimental and control subjects consumed for seven days an additional 150 mg. per day of nicotinamide.
- (7) Both experimental and control subjects consumed for seven days an additional 15 mg. per day of riboflavin.

The solid lines represent an experimental subject and the broken lines a control subject.

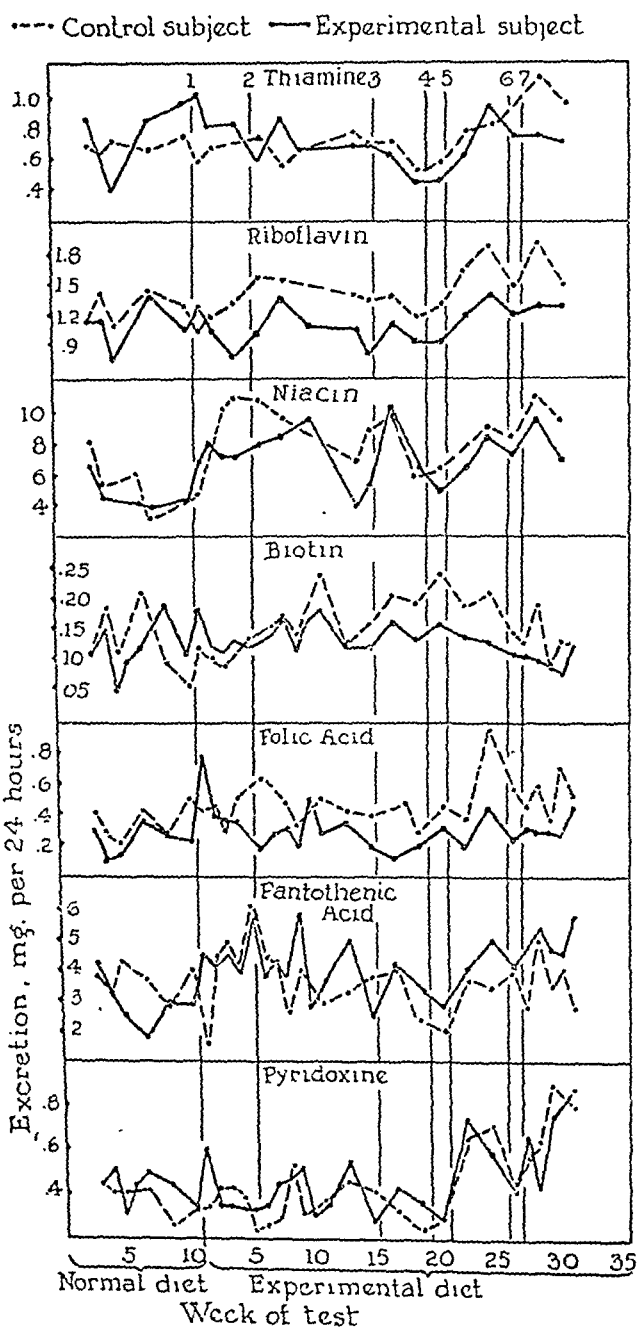


FIG. 1

maximum intake since consumption was not always one hundred percent. The diet consisted of foods frequently consumed in certain parts of the country such as corn meal in various forms (as fried mush, muffins and cookies) spaghetti, carrots, string beans, beets, gelatin, apples, pears, pineapple, salt pork, oleomargarine and sugar (7).

Supplementation for Control Subjects. For five weeks all seven subjects ate the restricted diet with no supplementation. At the beginning of the sixth week, and thereafter through the fifteenth week, all subjects were given daily by capsule 700 mg. calcium, 540 mg. phosphorus, 20 mg. iron and 666 I. U. vitamin D. In addition, the two subjects who were then chosen to act as controls were given daily in tablets the following crystalline supplements divided equally among the three meals: 1.2 mg. thiamine hydrochloride, 1.5 mg. riboflavin, 12 mg. nicotinamide, 60 mcg. biotin, 90 mcg. synthetic L. casei factor, 6.6 mg. racemic calcium pantothenate, 3.3 mg. dextro calcium pantothenate, 0.3 mg. para-aminobenzoic acid, 3 mg. pyridoxine hydrochloride and 1 gm. choline dihydrogen citrate. Corresponding placebos were given to the five restricted subjects. In addition, the controls were given in their food 45 grams per day of calcium caseinate (Casec).

Supplementation for Experimental Subjects. Beginning with the 16th week on the restricted intake, oral supplementation with vitamins and protein was begun for the five restricted subjects. Occasionally the vitamins were given intravenously also. Although the sequence of supplements varied for different subjects, the general plan was to add thiamine to the diet first, (and also to give it intravenously), followed by additions of protein (in the form of calcium caseinate) within 2-3 weeks. The supplements added next were niacin, then riboflavin, and then the lesser-known B-complex vitamins as a group (see above). The exact dates and types of supplementation are shown in graphs (fig. 1).

Fecal Collection and Analyses. Details of fecal collection and analytical methods are identical to those described in previous reports (5), (6).

RESULTS

The results indicate that with the possible exception of pyridoxine, the frequent changes in the level of vitamins found in the feces were not related to any one or any combination of the supplements. One possible exception to this was found in the case of one of the subjects whose fecal excretion level for each vitamin appeared to be increased following supplementation with that particular vitamin. It is the interpretation of the authors that in general, the fecal B-vitamins under discussion were influenced by factors other than the crystalline vitamins and protein that were added to the daily intake of food from time to time, pyridoxine possibly excepted.

With this interpretation in mind graphs (fig. 1) are presented as being representative of the over-all findings. These graphs present the data for two of the subjects, one control and one experimental, these being representative of each group. It is shown that of all the additions made by supplementation, niacin and riboflavin represent the only instance where a definite change appears to have occurred in the fecal vitamins, and that only in the case of pyridoxine. This was the case whether complete supplementation had been given for some 27 weeks (as in the case of the control subjects), or whether partial supplements had been given additively for shorter periods of time (as in the restricted subjects). This same effect was found to occur for all subjects.

In general it is believed that there was no interrelation between the addition of crystalline nutrients to the diet and the levels of various B-complex vitamins found in the feces. The possible exception referred to above, namely, pyridoxine, requires verification by a separate experiment, designed to permit the exclusive investigation of the relationship suggested in this work.

SUMMARY

Seven normal young volunteer male subjects ate for 38 weeks a diet which contained restricted quantities of B-vitamins and protein. Approximately twenty-seven per cent of the caloric intake was provided by cornmeal and other corn products. After five weeks, two of the subjects were chosen as controls and thereafter were given crystalline B-complex and protein supplements to equal the amounts usually found in a normal diet. No consistent relationship was found between this "complete" supplementation and the levels of fecal B-vitamins. The remaining five subjects were supplemented additively with individual B-vitamins and protein, beginning at 15-18 weeks. No consistent interrelationship was found to occur between any or all of these supplements and the levels of fecal B-vitamins, except possibly in the instance of pyridoxine. This latter possibility requires further investigation.

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A PARACOLON ORGANISM ANTIGENICALLY RELATED
TO THE SACHS Q-1030 BACILLUS AND ASSOCIATED
WITH CHRONIC ENTEROCOLITIS

MAJOR GEORGE F. LUTHPOLD, SN.C., A.U.S.*

Reports of paracolon organisms associated with acute diarrheas and dysentery-like infections are appearing with increasing frequency in the literature, and there are indications that the potential pathogenicity of certain paracolons is becoming more generally recognized.

The following report describes an unusual paracolon bacillus associated with many symptoms and findings of chronic dysentery in a case diagnosed as chronic enterocolitis, and touches briefly upon the clinical aspects of the case from which it was isolated. Also briefly discussed are the measures taken toward eradication of the paracolon organism and toward alleviation of symptoms presumably attributable to its infectious process.

BRIEF SKETCH OF CLINICAL HISTORY

The case of chronic enterocolitis with which this paracolon was associated was one of long standing, dating back to 1935 when the patient (CRD) contracted dysentery during an outbreak at an Army post. The etiological agent was not determined and the patient was not treated. He went on into a carrier state and had alternating diarrhea and constipation and a persistent dull pain in the right lower quadrant. During the ensuing 10 years the patient was hospitalized several times. He had his appendix removed but failed to experience any permanent relief. In 1943, neurological disturbances developed and became so marked that the patient was at one time diagnosed as a psychoneurotic. On our first contact with the patient in March 1945 he presented the picture of a chronically ill person, physically debilitated and mentally disturbed. He had been diagnosed as a hypochondriac. His

* From the Division of Typhoid Research, Army Medical School, Army Medical Center, Washington, D. C. With the technical assistance of Milton Toporek, B.A., M.A.

intestinal symptoms had not been treated because no pathogen had been found in his stools. Being himself a physician, he requested a course of one of the sulfa drugs, but was refused on the basis of the diagnosis—that his symptoms were functional in origin and, until an etiological agent in the form of an intestinal pathogen was found, specific treatment could not be prescribed.

BACTERIOLOGICAL INVESTIGATION

Considering this a research problem, amebiasis was first ruled out. Repeated examinations of the patient's stools revealed no protozoan parasites. Bacteriological cultures of stool specimens yielded the normal flora of *Esch. coli* on EMB (eosin-methylene-blue) and DC (desoxycholate-citrate) media; but on SS (Shigella-Salmonella) plates there appeared from 20 to 30 colorless colonies. The difficulty of standardizing stool-culture technique for quantitative determinations is recognized; nevertheless, by following the procedure outlined below, we were able to obtain close agreement in numbers of colorless colonies on SS agar in day-to-day cultures of the patient's stool:

One gram of feces was thoroughly emulsified in 3 cc. of plain broth. One-tenth cc. amounts of this emulsion were placed on EMB, DC, and SS agar plates and spread uniformly over the surfaces. Colorless colonies appeared well separated from one another on the last named medium.

That these suspicious colonies represented the same organism in day-to-day isolations was presumptively proven by biochemical reactions; but to more satisfactorily identify this organism, an antiserum was prepared early in the investigation and employed for all subsequent identifications. Because of its biochemical behavior, described below, this organism was designated "paracolon D", the "D" having no significance other than one to identify the organism with the patient, CRD.

CHARACTERIZATION OF THE ORGANISM

Morphological and Cultural Characteristics of Paracolon D. Morphologically, paracolon D was a non-motile Gram-negative rod. Although not detected on EMB and DC isolation plates, this organism grew well on these media after primary isolation on SS agar. On Russell's double sugar it produced an alkaline slant with acid and gas in the butt—typical of the paratyphoids. Subcultures on infusion agar made over a period of two weeks became somewhat mucoid in consistency, suggesting encapsulation of the organisms.

Biochemical Activity of Paracolon D. Paracolon D fermented aerogenically the following substances during a 7-day observation period: Glucose, maltose, lactose (2% gas), mannitol, xylose, arabinose, rhamnose, salicin, sorbitol, trehalose, dextrin, levulose, galactose and glycerol. Lactose and salicin fermentations were delayed for from 3 to 5 days, but the other substances were fermented rapidly. Sucrose, dulcitol, inositol, raffinose, and inulin were not fermented.

This organism was found to produce indol but not H_2S . It was methyl-red positive and Voges-Proskauer negative, and utilized citrate and d-tartrate. Its IMViC formula (1) would therefore read # #-# and the organism would be classified as a paracolon *Escherichia*.

Antigenic Composition of Paracolon D. By far the most interesting feature of paracolon D was its antigenic composition. First, to insure that we were not dealing with an aberrant form of the patient's common colon organism, we used the latter in agglutination tests with the paracolon D serum prepared early in this investigation. Paracolon D serum, although its titer for the homologous organism was 1:5120, failed to agglutinate the patient's *Esch. coli* in dilutions as low as 1:10. Whatever its composition, paracolon D was not even remotely related to its *Esch. coli* co-inhabitant. Since many of the so-called *Salmonella* antigens have been found in paracolons, paracolon D was typed with a complete set of diagnostic *Salmonella* sera, with negative results throughout. But when typed with *Shigella* sera, paracolon D was rapidly agglutinated by serum prepared with the Q-1030 strain of non-mannitol fermenters described by Sachs (2). Following this lead, cross-absorption

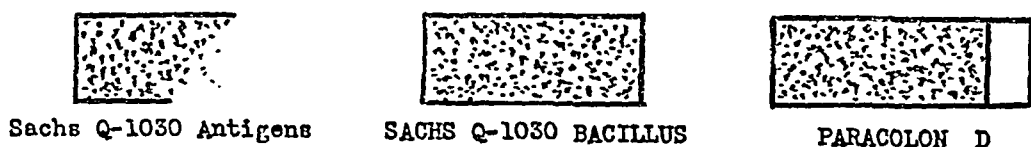


FIG. 1

tests were performed, revealing that although paracolon D organisms completely absorbed the Sachs Q-1030 serum, Sachs Q-1030 organisms failed to completely absorb paracolon D serum. In short, it appears that paracolon D possesses all of the antigens of the Sachs Q-1030 bacillus as well as some minor antigens of its own.

Diagrammatically represented, the two organisms would appear to bear the antigenic relationship illustrated in figure 1.

Immunogenic Relationship Between Paracolon D and the Sachs Q-1030 Bacillus. Since it does not always follow that full immunogenic relationships can be predicted on the basis of agglutinogenic components (3), cross-immunization tests were performed in mice with vaccines identically prepared from the two organisms in question. Details and results have been included in table 1.

It will be seen that these two organisms are immunogenically very similar. Either one, prepared as a vaccine, confers as much protection against the other as it does against itself.

Biochemical Dissimilarities of Paracolon D to the Sachs Q-1030 Bacillus. The discordant feature of the intimate agglutinogenic and immunogenic relationship between paracolon D and the Sachs Q-1030 bacillus is the wide disparity in their biochemical activities. This is best illustrated in table 2.

Somewhat similar incongruous relationships between coliforms and the *Shigella* have been reported. Smith (4) described a coliform organism which was antigenically identical with the Flexner type of *Sh. paradysesterae* and which attacked

the same sugars as the latter but with the production of gas. Paracolon D and the Sachs Q-1030 bacillus, however, present a different situation by exhibiting strikingly dissimilar preferences for fermentable substances, aside from the production of gas in these by paracolon D only.

TABLE 1

CHALLENGING ORGANISM	DOSES OF CHALLENGING ORGANISM (NUMBERS OF ORGANISMS)	RESULTS OF INJECTING THE DOSES OF ORGANISMS INDICATED IN COLUMNS ON THE LEFT INTO MICE WHICH HAD 7 DAYS PREVIOUSLY RECEIVED 0.5 CC. AMOUNTS OF THE VACCINES DESIGNATED BELOW, (EXPRESSED AS NO. OF DEATHS/NO. OF MICE)	
		Paracolon D vaccine	Sachs Q-1030 vaccine
Paracolon D	10 ⁷	0/6	0/6
	10 ⁸	4/6	5/6
	10 ⁹	6/6	6/6
Sachs Q-1030	10 ⁵	0/6	0/6
	10 ⁶	1/6	4/6
	10 ⁷	5/6	6/6

TABLE 2

FERMENTABLE SUBSTANCE	PARACOLON D	SACHS Q-1030 BACILLUS
Dextrose.....	AG	A
Mannitol.....	AG	—
Lactose.....	AG	—
Sucrose.....	—	—
Maltose.....	AG	—
Xylose.....	AG	—
Arabinose.....	AG	A
Dulcitol.....	—	A
Rhamnose.....	AG	—
Sorbitol.....	AG	A
Inositol.....	—	—
Salicin.....	AG	—
Indol.....	#	—
Citrate.....	#	—

Note: A: acid only; AG: acid and gas; —: negative; #: positive.

TREATMENT OF PATIENT

Sulfaguanidine. The patient was first treated for eradication of paracolon D on April 3, 1945. At this time he was placed on a course of sulfaguanidine consisting of 21 grams daily for 3 days, then 15 grams on each of 5 successive days. The patient reported a decrease in severity of pain in the right lower quadrant during the latter part of the treatment period and for a few days thereafter; also, that only formed stools were passed during this period. But, by the time the first follow-up cultures were made (10 days after treatment) loose stools and pain in the right lower quadrant had returned to the before-treatment status. Cultures of stool specimens

collected April 20 and 21 revealed that paracolon D was still present, though in somewhat fewer numbers.

Sulfadiazine. On April 24, the patient was placed on a course of sulfadiazine, 1 gram every 4 hours for 8 days, then 0.5 gram at the same interval for 5 days. A sulfa blood level of 11 to 12 mg. per cent was maintained during the last few days of treatment. The patient reported complete cessation of pain in the right lower quadrant 4 days after treatment was begun, and the passage of only well-formed stools. Recurrence of the pain was noted about 2 weeks after treatment. Cultures of the patient's feces were made frequently during the administration of sulfadiazine and for one week thereafter. A rapidly progressive reduction in numbers of paracolon D occurred during the period of treatment: on the last seven days there were 5 negative cultures while each of the 2 remaining cultures yielded 1 colony. Very shortly after treatment, however, paracolon D had returned in its usual numbers.

This was our last contact with the patient until November 1945. At that time he was again hospitalized in an Eastern hospital after two intervening hospitalizations during the summer and fall. He was still suffering from the gastro-intestinal symptoms and accompanying pain in the right lower quadrant, as well as from the neurological symptoms mentioned earlier in this communication. Upon being consulted by the medical service of the hospital where the patient was lastly under observation, for information on the intestinal bacteriology and for recommended treatment, a combined therapy of streptomycin and autogenous vaccine was suggested.

Sulfasuxidine. Streptomycin was then not available, but in lieu thereof the patient was given a course of sulfasuxidine, 2 grams every 4 hours, from January 3 to 13, 1946. Only three opportunities were afforded us for making reliable cultures of the patient's stools: On December 17, on January 5 (during sulfasuxidine treatment), and on January 28, 15 days after the course of the sulfa drug. Paracolon D was found on each of these occasions.

Autogenous Vaccine. A vaccine was prepared from a freshly isolated culture of paracolon D, phenol-killed without previous heating, and standardized to contain 1,000 million organisms per cubic centimeter.

The patient was given an initial course of 4 intradermal doses (0.1 cc., 0.1 cc., 0.2 cc., and 0.2 cc.) spaced by intervals of 5 days, followed two weeks later by 0.1 cc., and another 0.1 cc. after an additional two weeks. An allergic reaction was guarded against by preliminary sensitivity tests with 1:1,000 and 1:100 dilutions of the vaccine. The course of vaccine was initiated on November 23, 1945, and terminated on January 11 of the present year (1946).

In order to determine the patient's antibody response to the vaccine, mouse-protection and agglutination tests were performed with specimens of his serum collected at 10- to 14-day intervals during the vaccination period. Details and results of these determinations have been included in table 3.

CLINICAL PROGRESS AND FURTHER TREATMENT

During the last year of his illness, the patient experienced no relief from his symptoms (except that noted during sulfa treatment above) until the

latter part of December 1945. At this time he reported that he felt better generally; he was more active, aggressive, and optimistic; and his stools had become less frequent and of normal color and consistency. He had recovered his normal appetite, and he was gaining weight. On January 5, 1946 he reported that his temperature was never above 98.4° F., whereas he had been running a low-grade fever for months prior to treatment. His pulse after meals ranged from 80 to 90, whereas formerly it had been from 110 to 120. He further reported that his head felt clearer, that he experienced few or no headaches, and that he was actually 15 pounds heavier than he was last November. A final diagnosis of "Colitis, chronic, moderate, associated with positive stool cultures for paracolon D" (5) was made by his ward physician; and, at the completion of his case the patient's condition was evaluated as

TABLE 3

SPECIMEN OF SERUM (IN REFERENCE TO TIME OF COLLECTION)	RESULTS OF INJECTING THE DOSES OF PARA- COLON D INDICATED BELOW INTO MICE WHICH HAD 1 HOUR PREVIOUSLY RECEIVED 0.05 CC. AMOUNTS OF THE SERA DESIGNATED ON LEFT. (EXPRESSED AS NO. OF DEATHS/NO. OF MICE)				PROTECTIVE TITER (EXPRESSED AS MLD'S AGAINST WHICH THE SERUM PROTECTED)	AGGLUTINATIVE TITER
	10 ⁵	10 ⁶	10 ⁷	10 ⁸		
Nov. 23.....	0/4	2/4	4/4	4/4	10	1:80 (#)
Dec. 3.....	0/4	1/4	4/4	4/4	10	1:80 (#)
Dec. 13.....	0/4	0/4	4/4	4/4	100	1:160 (#####)
Dec. 27.....	0/4	0/4	0/4	4/4	1000	1:160 (#####)
Jan. 10.....	0/4	0/4	0/4	4/4	1000	1:160 (#####)

Note: MLD of freshly isolated culture of paracolon D was 10⁴ (10,000) organisms.

"Improved" (5). A disposition board met on January 15 and recommended that patient "formerly classified in a temporary limited military status, be returned to full military status" (5). Accordingly, the patient was returned to full duty. By the middle of March, he felt so greatly improved that he considered himself as cured.

During the latter part of April, however, the patient experienced a return of abdominal pain, loose stools, and headache. He was given a stimulating dose of vaccine on April 24th, at which time the paracolon was found in his stool cultures. It was evident that the patient was suffering from a relapse and that eradication measures were imperative for permanent relief.

Streptomycin. Streptomycin became available on May 17th, and the patient was placed on a course of the antibiotic consisting daily of 2 g. in 4 divided doses orally, and 2 g. in 5 divided doses intramuscularly for 15 days. Relief from intestinal symptoms became noticeable 5 days after treatment was initiated, and paracolon D has been absent in stool cultures up to the present time. It is believed that the paracolon has been permanently removed,

and that the patient is now cured of his intestinal infection and of some of the attendant symptoms.

DISCUSSION

The Paracolon. Patient CRD had evidently been suffering for an indefinite time from a chronic infection of the lower gastro-intestinal tract, the etiological agent of which was a paracolon bacillus. This organism, classified on the basis of its biochemical characteristics, is a paracolon *Escherichia*; but antigenically it is intimately related to a member of Sachs' group of non-mannitol fermenting dysentery bacilli—namely, strain Q-1030 (2).

Reference has already been made to Smith's (4) description of a coliform organism which was antigenically identical with a Flexner type of *Sh. paradyenteriae*. This worker also described a gas-producing dissociate of the Flexner type organism. Stuart, Rustigian, Zimmerman, and Corrigan (6) reported on *Esch. coli* organisms which were antigenically identical with or closely related to *Sh. alkalescens*. Zimmerman (7) studied a coliform which was antigenically related to *Sh. sonnei*. Ferguson and Wheeler (8) quite recently reported on two paracolon cultures that shared minor antigens with the Flexner group, and a non-reciprocal relationship to Boyd's strain P-143. The most recent report we have seen in this connection is the paper by Wheeler and Stuart (9), in which are described two paracolon organisms (one from a food handler, the other from a case of acute diarrhea) which had the identical somatic antigen of the Sachs Q-771 strain of non-mannitol fermenters (2).

It might be mentioned here that much doubt was cast on the etiological role of paracolon D by individuals responsible for treatment of the patient, chiefly because it was, biochemically, a paracolon and thus failed to conform to the generic description of well-established enteric pathogens. Consequently, adequate treatment for the infection was delayed for months. Fortunately, this refractory attitude toward accepting paracolons (particularly *Escherichia* paracolons and intermediates) as potential pathogens is gradually yielding to a broader concept of their importance in intestinal infections and intoxications.

Concerning the case in question, proof of an antigenic and immunogenic relationship to a recognized dysentery bacillus, fully reciprocated as it was between paracolon D and the Sachs Q-1030 organism, should be sufficient grounds for removing any doubt as to the potentialities of paracolon D and for classifying this organism as an enteric pathogen.

It is proposed that paracolons found under suspicious circumstances be typed for *Shigella* antigens, regardless of what relationship to other genera (*Salmonella* or *Shigella*) might be suggested by their biochemical activities. Such a study was reported by Felsenfeld and Young (10), who used a poly-

valent serum prepared against *Sh. dysenteriae*, *Sh. ambigua*, *Sh. sonnei*, *Sh. alkalescens*, *Sh. paradysenteriae* V, W, Z, and Boyd 103, and 2 strains of *Sh. dispar* (11). Only 2 of 1200 paracolons examined possessed a composition related to any of the antigens employed in the production of the polyvalent serum used by Felsenfeld and Young. However, in view of the incomplete coverage represented by this polyvalent serum, it is believed that an extension of this study, to include examinations for antigens of the Boyd and Sachs strains, would shed additional light on the problem and would more clearly point out the position of paracolons among the Gram-negative enteric pathogens.

Treatment. The rationale of the treatment recommended by us (streptomycin and autogenous vaccine) was based first upon the desirability of eradicating paracolon D from the patient's gastro-intestinal tract; and, secondly, in the event that attempts at eradication failed, on the necessity of fortifying the patient's immunological defense against the paracolon and its absorbed products.

The parenteral administration of an autogenous vaccine increased appreciably the patient's immunological defense against paracolon D, as evidenced by increased protective titers of the patient's blood serum from 10 MLD to 1,000 MLD. Eradication of the organism by vaccination alone, although reported by some workers as successful in certain cases of intestinal carriers, was scarcely hoped for in the case under discussion in which the paracolon was, apparently, securely entrenched. The vaccine therapy was intended primarily to equip the patient immunologically to combat the infectious process of paracolon D, thus permitting him to live on terms with his parasite just as simple symptomless carriers do. In this, vaccination was apparently successful but only as a temporary expedient. What probably occurred was that the paracolon, at first suppressed by the protective antibodies arising from vaccination, as manifested by the patient's improvement for many weeks, gradually acquired a resistance to the antibodies and once more became capable of assuming its former pathogenic role.

CONCLUSIONS

1. Patient CRD was suffering from a chronic intestinal infection (chronic enterocolitis) the etiological agent of which was a paracolon organism closely related antigenically to the Q-1030 strain of non-mannitol fermenting dysentery bacilli described in 1943 by Sachs.

2. Parenteral administration of an autogenous vaccine produced an appreciable increase in the patient's serum protective titer against the paracolon he was harboring, coincidental with a definite clinical improvement in the patient's general condition. It is believed that vaccine therapy served as a satisfactory

temporary expedient in alleviating the patient's symptoms; but, at best, vaccination was only a compromise between no treatment at all and an effective eradicated treatment directed toward the offending paracolon bacillus.

The paracolon obviously was sulfa-resistant, but yielded to a course of streptomycin.

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· MASSIVE GASTRIC HEMORRHAGE ASSOCIATED WITH ABERRANT PANCREAS IN THE STOMACH

BERNARD M. CHAPMAN, M.D., WOLFGANG F. VOGEL, M.D., AND THEODORE P. SCHOMAKER, M.D.

INTRODUCTION

Pancreatic tissue occurring in an aberrant location has been referred to in the literature by various terms. Opie (1) refers to it as an accessory pancreas. Clarke (2) as myoepithelial hamartoma, and Barbosa (3) as pancreatic heterotopia.

An increasing number of cases are being reported in the literature since the first authentic case by Klob (4) was reported in 1859. Warthin (5) in 1904 reviewed 47 cases to which he added two. Moore (6) in 1929 reported 155 cases in the literature and added another case. The most recent review by Barbosa in May 1946 brought the number of reported cases to 470. However, an additional three cases not included in Barbosa's review and reported by Marshall and Aronoff (7) have been found. These, together with the authors' case, bring the present total number of reported cases to 474. The increase in the number of cases reported in recent years is due to finer diagnostic measures, and a greater attention to microscopic investigation of tumors and nodules found in routine autopsies.

Of 474 known cases of aberrant pancreatic tissue 124, or 28.3%, have occurred in the stomach. Of 467 consecutive gastric tumors reported by Marshall and Aronoff in 1944 only 12 were found to be benign tumors, and of these three were aberrant pancreatic tissue. Of 41 cases of aberrant pancreatic tissue reported by Barbosa 61% were discovered at operation. In thirteen of these cases the tumor was found in the wall of the stomach, and gastro-intestinal symptoms were noted in ten of these. It thus becomes apparent that aberrant pancreatic tissue of the stomach must be considered in the differential diagnosis of intragastric lesions, especially where the diagnosis of a benign gastric tumor is involved.

There are many theories as to the embryological origin of aberrant pancreatic tissue. Moore believes that different factors appear as the cause of origin in different cases. In some cases inflammatory or embryonal adhesions with subsequent detachment of a mass of pancreatic cells may be the cause. In others, the development of primary anlage of Zenker (8) or Glinski (9) or secondary snared off anlage of Wharton may be a factor. Moore offers the conception that the cells of this anlage are still undifferentiated entoderm and capable of differentiating into pancreatic acini. Islands of Langerhans, ductal epithelium, and glands of Brunner.

Morphologically the aberrant gland is located most often in the submucosa of the stomach. It also can be located in the muscularis or serosa. In the case here reported two nodules were submucosal, the other subserosal. The histological picture of aberrant pancreas is most often the same as the pancreas itself with acini forming lobules and ducts and Islands of Langerhans. Numerous cases have been reported where one or more elements of a normal pancreas were absent. Barbosa does not believe that there is any direct relation,



FIG. 1. PHOTOMICROGRAPH, LOW POWER, THROUGH NODULE IN WALL OF STOMACH

In the upper margin of the section can be seen gastric glands below a continuous layer of Bruner's glands arranged in the form of lobules. Opposite arrow in submucosa can be seen a group of pancreatic ducts one of which is anastomosing with a Brunner's gland. Below this in the muscularis are lobules of the aberrant pancreatic tissue with clusters of pancreatic ducts. The pancreatic lobules, especially that on the left, show evidence of chronic inflammatory changes.

continuity or transition between the glands and ducts of the overlying mucosal epithelium and the acini and ducts of the aberrant pancreatic tissue. However, in our case numerous instances of anastomosis between pancreatic ducts and Brunner's glands can be seen histologically. One such example is shown in figure 1.

Pathological changes can occur in aberrant pancreatic tissue and in the surrounding tissues. The most common change is chronic interstitial pancreatitis. Gibson (10) reported a case with acute pancreatitis. In a few instances neoplastic changes in the aberrant pancreatic nodule are recorded (11, 12). The case reported here is the first in the literature of acute hemor-

rhagic pancreatitis taking place in an aberrant nodule in the stomach, associated with ulceration of the overlying mucosa and leading to gastric hemorrhage.

CASE REPORT

The patient, a 22 year old soldier, of American Indian extraction, was admitted to the medical service of the hospital. The past history was as follows. On 1 October 1945 he was hospitalized in a field hospital on Mindinao, P. I., because of malaria and a supposedly coexisting jaundice. He was discharged as cured after two weeks, and remained well until early in December 1945 when he was on a troop transport on the Pacific homeward bound. After a few days at sea he developed a chill and fever and reported to sick bay. It was thought that the symptoms were due to malaria, and after proper therapy was instituted he had no further fever attacks. On the 11th of December 1945, while still in the ship's hospital but greatly recovered from the fever, he noticed a sudden sharp pain in the epigastrium which lasted for about five minutes. Soon after, he had two or three episodes of bloody and coffee grounds vomitus. The next day he vomited blood a few more times, and also noticed some tarry stools. When the ship docked he was immediately hospitalized.

On closer questioning the patient gave a history of having had epigastric distress since 1944. He had had a mild aggravation of these abdominal pains since going overseas. The patient had a mild diarrhea of six weeks duration while on Mindinao in September and October of 1945.

Physical examination was essentially negative except for a mild icteric tinge to the skin which was believed to be due to atabrin. X-ray examinations of the chest revealed some fibroid calcified lesions in the left apex, believed to be tuberculous in nature and completely arrested. Three sputum examinations were negative for tubercle bacilli. A gastro-intestinal series revealed a mass 3.5 cm. in diameter on the greater curvature of the stomach opposite the incisura with a small crater at its apex (fig. 2). This was interpreted as being a possible leiomyoma or gastric polyp. Gastroscopy revealed a benign submucosal tumor of the greater curvature in the antrum of the stomach. This diagnosis was made because the mucous membrane covering the tumor appeared normal and as if it were raised into the gastric lumen by a submucosal growth. The summit of the lesion appeared notched, but no break in the mucous membrane was seen. These findings supported the diagnosis of a benign gastric tumor which gave rise to severe gastric bleeding. Surgery for this condition was advised. At celiotomy on 20 March 1946 in the stomach on the greater curvature at the junction of the antrum and the corpus a firm nodule measuring 3 cm. in diameter was felt through the stomach wall. It had an elastic, rubbery consistency. A similar, 5 x 2 mm., nodule on the posterior wall of the stomach just proximal to the pylorus was likewise detected and just opposite the pylorus on its inferior surface another nodule measuring 3 cm. in diameter and appearing to be subserosal was also found. The stomach was opened and under direct vision the mucosa was incised over the smallest of the nodules. The lesion was submucosal, yellowish in color, but did not shell out readily. The same was true of the larger

lesions. It was decided, therefore, to do a subtotal gastrectomy that would include all of the lesions found. The patient made an uneventful post-operative recovery.

The patient consistently showed an eosinophilia ranging from 20% to 62% and found to be present on ten blood counts performed between December 1945 and May



FIG. 2. BARIUM MEAL X-RAY OF STOMACH. SHOWS FILLING DEFECT ON GREATER CURVATURE OF STOMACH WITH SMALL CRATER AT ITS APEX

1946, all preoperatively. A careful history and search for clinical manifestation of allergy was negative. Thirteen stool examinations were consistently negative for parasites, ova or amoeba. Muscle biopsy and sigmoidoscopy were non-revealing. Empirically caprocol was given in February 1946 but failed to affect the eosinophilia.

This was followed by two injections of mapharsen which has been suggested as treatment for tropical eosinophilia. Nevertheless, the blood picture remained unchanged.

The pathological report on the specimen follows. The specimen consists of the distal half of the stomach and portion of the duodenum measuring 8 x 16 cm. In



FIG. 3. PHOTOMICROGRAPH, HIGH POWER, THROUGH MARGIN OF ULCER IN THE STOMACH

Floor of ulcer lined by Brunner's glands and granulation tissue. There is a dense inflammatory infiltration composed of round cells, plasma cells, eosinophiles and neutrophiles into the gastric mucosa and underlying submucosa and Brunner's glands.

the anterior wall of the stomach, 6 cm. proximal to the pylorus, is a lesion in the wall measuring 3 cm. in diameter and 1 cm. in thickness. The lesion is yellowish tan in color, and somewhat lobulated. It seems to arise in the muscularis and bulges into the submucosa, lifting the mucosa above it for a distance of 1 cm. The mucosa overlying this tumor mass is umbilicated and in the umbilication there is an area of ulceration measuring 2 mm. in diameter. At this point the mucosa is attached to

the underlying tumor. There is another area in the posterior wall of the stomach 1 cm. from the pylorus, which measures 5 x 2 mm. This nodule also seems to arise from the muscularis and bulges into the submucosa. Along the greater curvature of the stomach, opposite the pyloric ring and at its inferior surface, there is another lesion measuring 2.6 cm. in diameter which seems to arise from the muscularis and bulges into the serosal surface. At first glance it resembles a lymph node, but on closer inspection it is found to be grayish tan in color and lobulated, resembling the lesions described above. The mucosa of the duodenum and the stomach, except for the area of ulceration, is normal. Microscopically the section from the nodule of the



FIG. 4. PHOTOMICROGRAPH SHOWING ABERRANT PANCREATIC TISSUE IMMEDIATELY BELOW ULCERATION IN GASTRIC MUCOSA

Many acini are broken up, digested, necrotic and separated widely by a dense inflammatory and hemorrhagic extravasation.

stomach is lined by gastric mucosa which shows a slight polypoid arrangement. In the section taken through the umbilicated area of the largest lesion the gastric mucosa is seen to be ulcerated (fig. 3). The base of the ulcer is lined by granulation tissue which is being converted into dense fibrous connective tissue and overlies Brunner's glands. The gastric mucosa surrounding the ulceration is densely infiltrated with eosinophiles, polymorphs and plasma cells. The submucosa is also the site of subacute inflammatory changes. It is slightly edematous, infiltrated with round cells and eosinophiles, and contains Brunner's glands arranged in lobules (fig. 1). The Brunner's glands overlie the pancreatic nodule beneath. A good sized area of this pancreatic tissue measuring approximately 3 mm. in diameter is the seat of acute hemorrhagic pancreatitis (fig. 4). Many of the pancreatic acini are necrotic

and have undergone autolytic degeneration. Between the distorted acini there is marked interstitial hemorrhagic infiltration. There is also a marked infiltration of polymorphs, plasma cells and eosinophiles. In some fields regenerating pancreatic acini can be seen. The pancreatic tissue around this area appears fairly normal. This pancreatic tissue fills up the submucosa and extends deep into the muscularis. The pancreatic tissue contains acini arranged in the form of lobules (fig. 5). The acini appear to be functioning and contain colloid material. The pancreatic ducts are arranged between the lobules at normal intervals and there are well formed Islands of Langerhans. Some small lobules of pancreatic tissue are seen away from the main



FIG. 5. PHOTOMICROGRAPH, HIGH POWER. SHOWING NORMAL APPEARING PANCREATIC TISSUE IN PANCREATIC NODULE

Note acini arranged in lobules and interlobular pancreatic ducts. A few well developed Islands of Langerhans can be seen. Acini appear functioning and contain eosinophilic staining colloid material.

mass of the tumor and are completely surrounded by the smooth muscle of the muscularis. This is also true of the pancreatic ducts which in some sections show five to eight ducts in one mass surrounded by muscular tissue. In many of the sections a direct anastomosis between a pancreatic duct and Brunner's glands can be seen (fig. 1). The lesion opposite the pylorus is similar except that the mass of pancreatic tissue lies below the muscularis and protrudes into the serosa. However, smaller nodules of pancreatic tissue are found in the muscularis and even in the submucosa. In these sections anastomosis between pancreatic ducts and Brunner's glands can also be seen. There is no evidence of pancreatitis in this nodule. Sections of lymph nodes in the greater curvature of the stomach show evidence of chronic nonspecific inflammatory changes with a moderate infiltration of eosinophiles.

Pathological Diagnosis: 1) Aberrant pancreatic tissue in the wall of the stomach. 2) Acute pancreatitis of one nodule in the stomach with ulceration of gastric mucosa overlying it.

SUMMARY AND CONCLUSIONS

This is the first case reported of aberrant pancreatic tissue in the stomach which produced a syndrome of epigastric distress with massive gastric hemorrhage. It is believed that the latter was secondary to acute pancreatitis in the aberrant pancreatic nodule with secondary ulceration of the gastric mucosa overlying it with resulting hemorrhage.

The aberrant pancreatic tissues in the stomach were overlaid with Brunner's glands which are normally found only in the duodenum. This tends to support the theory of splitting of the pancreatic anlage from the duodenum in the primitive gut. Definite anastomoses between pancreatic ducts and Brunner's glands in the submucosa are shown.

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EDITORIAL

CURIOUS WAYS IN WHICH CERTAIN DISEASES ARE STOPPED

In Rackeman's recent review of the literature on Allergy (*Arch. Int. Med.* 77: 718, 1946) he remarked that an attack of jaundice will relieve asthma and keep it from returning for some time. This fits with the studies of Hench and others who have noted that jaundice in some miraculous way relieves severe and painful arthritis, and it fits with the observation that jaundice is a good cure for migraine. The fact that in a case of crippling arthritis the complete relief of great pain and disability came several days before the jaundice appeared, showed that the essential feature was not the cholemia but the primary injury to the liver. Similarly, Morlock and the writer found that the coming of cirrhosis of the liver, without jaundice, can for some time keep a migrainous person from having sick headaches.

As Rackeman suggested, all of this may fit in with Manwaring's (1921) old observation that a dog sensitized to some allergin cannot react anaphylactically to that substance after its liver has been shunted out by means of an Eck fistula. One wonders also if the remarkable relief that many migrainous women experience during pregnancy, or for some time after an attack of typhoid fever or after an operation, might be due to some temporary impairment of liver function. Curious is the fact that many women who experience perfect relief from migraine in one pregnancy will not get relief in another.

Hench and others have tried in various ways to produce a jaundice which will cure arthritis without hurting the patient, but so far without entire success. It is to be hoped that some day a drug may be found which will depress some function of the liver and in so doing will work the desired miracle of healing in cases of arthritis, asthma and migraine.

Another curious phenomenon well known to gastro-enterologists is the prompt disappearance of all ulcer distress following a big hemorrhage from the lesion. That such bleeding has some desensitizing effect on the whole body is suggested by the fact that when the patient suffers also from migraine, hematemesis may bring him a good vacation from that disease too. Still another puzzling observation is that a permanent cure of severe migraine sometimes follows a small stroke.

The editors of *Gastroenterology* would be pleased if when physicians observe curious phenomena of this type they would write a letter describing them. Out of a collection of such observations might well come hints of great value in the treatment of certain diseases.

W. C. A.

COMMENT

BRUCELLOSIS VERSUS NEUROSIS—AN ATTEMPT AT AN APPRAISAL

Today gastro-enterologists are seeing quite a few women with an old story of what looks like ordinary neurosis and constitutional inadequacy, but with a recent diagnosis of brucellosis. Usually this has thrilled the woman and filled her with the conviction that if only she could get some streptomycin, she would be well and strong and done with all her troubles.

Although the wise physician will have his doubts about all this, he will also be willing to admit that perhaps there is something in this excitement about brucellosis; perhaps he is missing the diagnosis in many cases, and so he will keep an open mind and will watch for some exact information on the subject. Perhaps, however, he will wonder why it is that in his state there is one physician who is seeing all the cases of "brucellosis." Could this physician perhaps be a bit wild and overly enthusiastic?

The subject of brucellosis can be studied under two headings: one of the usually vague, chronic form, and the other of the often definite, acute form. As already intimated, a few physicians in the United States today are inclined to diagnose as brucellosis practically any nervous state or anything else to which no one can give a clear-cut medical name.

A physician can examine very carefully a score of such patients with an afternoon temperature of 99.4° F. and be unable to find one with brucellosis, that he can be sure of, or at least so sure of that he would dare to present the case before a medical society.

Usually in these cases the diagnosis is based on only one report of a positive agglutination of *Brucella abortus* by the patient's blood. When the agglutination test is repeated by a good bacteriologist, in almost all cases, the report is that in order to get a positive result the blood had to be only slightly diluted. The revised report, therefore, is "clinically negative."

The acute febrile stage of the disease is seldom seen by the medical consultant. Dr. Wendell H. Hall has discussed the problem ably in the July, 1946, number of *Minnesota Medicine*. He noted that it is curious that infants and children seldom seem to get the infection, when they are more exposed to infected milk than is anyone else. Actually, the disease is met with most commonly among the middle aged. The majority of these persons are farmers who handle animals, the employees of packing plants who handle the flesh of infected animals and housewives and domestics who also handle meats.

According to Hall, the onset of the disease may be insidious or sudden.

It may begin with a chill and high fever, or more often it will start with malaise, headache, pain in the back or legs, sweating and a low grade fever. The most common symptom complained of is weakness. The term "undulant fever" is a misnomer because as Hall and Spink found, when the fever appears it is usually not undulant. Curiously, in some instances, fever may be entirely absent even in the presence of bacteria in the blood.

In only about a third of the cases can one depend on finding a large spleen, and in perhaps 10 per cent of the cases the lymph nodes are enlarged. In a few instances one can get evidence of localization of the organisms upon a heart valve or in the gallbladder or in some bone. In some cases there is a characteristic clouding of the roentgenograms of a vertebral body.

Unfortunately, there are no symptoms or signs that are specific for the disease; hence the clinician must depend largely on the laboratory for a confirmation of his hunch. But even here considerable confusion exists. There may be a mild anemia, but this is not characteristic. The leukocyte count may be normal or slightly below normal and there may be a little excess of lymphocytes. Curiously, the erythrocyte sedimentation rate is likely to be normal or only slightly increased. The presence of agglutinins for *Brucella abortus* in the blood serum is one of the most reliable findings, but difficulties in interpretation arise when the titer is low. It has been stated that a titer of 1:80 is diagnostic, but early in the disease, agglutination may be absent.

The complement fixation test, according to Hall, has no advantage over the agglutination test. Similarly, the new opsonocytophagic test does not seem to be sufficiently reliable for routine clinical use.

The finding of *Brucella* in the blood is, of course, the most convincing proof of the presence of the disease, but a positive culture is hard to get. In forty cases of what was diagnosed as acute brucellosis at the University of Minnesota Hospital, positive cultures were obtained in only a third.

Skin sensitiveness to *Brucella* antigen develops early in the course of the disease. The reaction is usually delayed, and it should be read after at least twenty-four or forty-eight hours. A positive skin test may be expected in nearly every case of active brucellosis, but its presence is no more reliable than that of a low titer of serum agglutination. Skin sensitiveness persists for years after clinical recovery from the disease. Except during the first few weeks of the disease a negative skin test may be said to rule out brucellosis. This is a good strong statement. An exception to the rule must be made in those rare cases in which the organisms have localized on a heart valve.

The presence of a positive skin test by itself is not sufficient evidence of active brucellosis. Recently 553 adults were tested in the University of Minnesota Hospital by Dr. George N. Asgaard. Of these, 104 had a positive intradermal test with purified *Brucella* protein, and twenty-three had ag-

glutinins in the serum. In only eight of these was there any clinical evidence of active brucellosis, and in only one patient was a positive blood culture obtained.

Interestingly, in one case Dr. Hall was able to isolate viable *Brucella* from an abscess around the gallbladder, *ten years after the onset of the disease*. In this respect the disease resembles typhoid fever.

Now in regard to the possible chronic form of the disease. In a recent article, Harris (1946) admitted that this is one of the most difficult diseases of all to diagnose. "There are no pathognomonic signs or symptoms. . . . Exclusion of other diseases often is as important as any other diagnostic method, unless positive culture of the organisms or a high blood agglutination titer is available." Harris cautioned the reader that "unless the diagnostician is wary, he may attribute to brucellosis all the symptoms which the patient exhibits, only to find later that in addition to brucella infection there is also a perhaps unrelated psychogenic or somatic illness. Conversely, before making a diagnosis of psychoneurosis one should be sure that brucellosis has been ruled out." As Harris went on to say, wisely, "When the neurosis and brucellosis co-exist, the patient often adds to the difficulty of the diagnostic problem by unwillingness to accept the role played by the emotional state." He might have added that in most cases it is most unkind to inject into the mind of a neurotic and psychopathic woman the idea that all her troubles are due to brucellosis.

Harris stated that all the tests leave much to be desired. He felt that the agglutination test is the most reliable. He maintained that a negative agglutination test does not rule out brucellosis. This view is unfortunate because it enables enthusiasts to feel justified in labeling any neurosis or psychosis as "brucellosis." Harris felt that a titer of 1:80 or higher can be considered adequate evidence of active infection. A majority of all cases of "chronic brucellosis" showed no agglutinins! This makes one wonder if in all these cases the diagnosis was not wrong.

"Even a positive skin test is of limited significance—it does not indicate the present status of the infection." It is like a positive tuberculin test. Much depends also on the choice of the antigen, the mode of its preparation, and the mode in which the test is performed. It will be news to many physicians that the cutaneous reaction should be read at the end of four days, and according to Harris, sometimes as late as the seventh day. Many workers have attached significance only to a violent cutaneous reaction. All that such a positive skin test means is that at some time the patient was sensitized to *Brucella* protein. He need not have had clinical brucellosis.

According to some experienced workers, notably Simpson (1941) and Spink (1945), the *opsonocytophagic* test deserves little confidence. There

are too many technical difficulties that can cause the result of the test to be unreliable. When it comes to blood culturing, the physician should remember that it is difficult to grow the *Brucella* organism, and hence special methods have to be used. One may have to use the method of guinea pig inoculation, and no report should be given before sixteen or eighteen weeks. The organism requires 10 per cent of carbon dioxide in the culture medium. The best medium is bactotryptose broth with agar or liver infusion broth with agar. Frequent subculturing is essential. A splenic puncture may reveal the organism.

If in the case of a frail, constitutionally inadequate woman the diagnosis of brucellosis would mean her prompt recovery under appropriate treatment, there would be much more reason for making this diagnosis in doubtful cases, but actually, as Harris admitted, there is no good specific treatment, and whatever treatment there is must be carried out for a minimal period of five years before a reasonable hope for cure can be entertained! This does not give the woman any great cause for rejoicing over her new diagnosis and crowing over the physicians who did not make it.

Many physicians have relied for treatment on fever, usually induced by the intravenous injection of typhoid vaccine, but as Harris said, this is not likely to help any because the *Brucella* is not even as susceptible to heat as is the gonococcus.

The sulfonamides and penicillin give no promise of curative value, but it is possible that streptomycin may be of value in some of the acute cases. Unfortunately it does not always cure the disease when given in large doses to guinea pigs, and hence it obviously is not going to be a marvelous cure for the neurotic woman who may or may not have the disease.

In his closing comment, Harris summed up the situation as the consultant often sees it today—as he said, “The patients’ unwillingness to abandon the solid ground furnished by an earlier diagnosis of a somatic illness for what they consider the less tangible and more onerous diagnosis of neurosis adds to an already complicated problem.” Under these circumstances it is usually a kindness not to give a psychopathic, constitutionally inadequate woman, who has had one illness after another for thirty years, the idea that all her troubles are due to brucellosis, that all the many good physicians who saw her throughout the years were incompetent, and that she could get well if only she could get enough streptomycin.

W. C. A.

BOOK REVIEWS

PEOPLE IN QUANDARIES—THE SEMANTICS OF PERSONAL ADJUSTMENT. *By Wendell Johnson.* Harper and Brothers, New York. 1946. pp. 532. Price \$3.75.

This is a most stimulating and thought-producing book. It was written by Dr. Johnson who is director of the University of Iowa Speech Clinic and professor in the Departments of Speech, Psychology and Child Welfare. He is editor of the American Speech Correction Association's Journal of Speech Disorders and Chairman of the Association's research-planning Foundations Committee, President of the Society for General Semantics, and Associate Editor of *Etc: A Review of General Semantics*.

The book is rather heavy reading and the impression is that the author could have boiled it down a great deal. The important thing is that here and there the physician will run onto gems of thought which can be of great use to him in his handling of nervous patients. For those physicians who would like to get some idea of what general semantics means, and what it means to the physician and the psychiatrist, and to everyone who would like to think clearly, this is a very helpful book. As Johnson shows, so much of the muddled thinking of both sane and somewhat insane persons is due to an inability to use language properly. So many persons are in miserable quandaries because their thinking is so confused. Often psychiatrists now are finding that if only they can get people to see through their problems clearly, and get them to see what they really want in life, they can be helped tremendously.

We physicians all know the type of patient who comes in and says he is miserable but cannot tell clearly what is the matter or what is his main complaint. As Professor Johnson says, so many persons feel that in some way they have failed of attainment and have failed to get satisfaction and happiness, but they are not clear as to what they really wanted in the way of success. He says many students at college, who are mal-adjusted, have what they call the I. F. D. disease, "from idealism to frustration to demoralization." So many persons have a great idealism but it is so vague that they cannot achieve success through it.

Professor Johnson says that many persons who haven't achieved the success they want get the idea that others are blocking their way, and hence they spend more and more of their available energy and time in hating these persons and trying to keep them from doing what they want to do. As every able man, who has ever worked in business or universities knows, there are any number of persons who, instead of working hard to forge ahead themselves, spend most of their energy watching the other men alongside of them and trying to pull them back and keep them from doing anything that will be outstanding.

As Johnson says, so much of success in life depends on being able to put clear-cut questions. There never can be a precise answer to a vague question. That is one reason why the man who attempts to get somewhere in this world must spend much of his life learning to talk and write clearly. He must find out what he wants and what he means and then express these things clearly. Professor Johnson thinks

that if we ever tried to express mental hygiene in one word it would be "accuracy." In order to get more accuracy into life, a number of men have been studying speech and what we mean by various words and phrases. As Doctor Johnson says, the trouble with so many persons is that they give rigid meanings to words and then are governed and hemmed in and kept from developing because of these words.

We physicians know the type of woman who says "I can never sit in the least draft," or "I can never touch oranges," or "I can never sit riding backward in a train." As Johnson says, we should avoid the words, "always" and "never."

So many of our troubles in this world are due to the naive belief that other persons use words in exactly the same way as we do, or accept the meanings that we give to certain words. So often because of this defect two people get into a fight and get to hating and distrusting each other because they were not arguing about the same thing.

Another great difficulty with most people is that to them things are either black or white; a man is either good or bad. The scientist knows that there are all gradations in practically every quality. The average man does not know how often exceptions must be taken. The scientist is always paying attention to exceptions to the rule. Johnson points out that these tendencies of ours to use words in the rigid way account for the fact that we can discuss dispassionately all sorts of things, but are likely to get into a fight, even with our relatives, when we try to discuss religion or politics. The trouble is that to some people a new dealer is a wonderful person, always right, and never able to do wrong. To the other person he is a scoundrel and a liar and a destroyer of democracy in America. To a professor of Economics a new-dealer might appear to be a fine, honest, public-spirited man, with many good ideas and much idealism but also some crack-pot ideas which have been tried out many times in the course of history with disastrous results.

Doctor Johnson, in the last half of his book, goes on to show how we physicians can help persons who are, as he says, "unsane" by getting them to see that so much of their trouble is due to their inability to think and speak clearly as the scientist would do. They are too full of the type of thinking that says that black is all black, and white is all white.

AMINO ACID ANALYSIS OF PROTEINS. By William H. Stein, Reginald M. Archibald, Erwin Brand, R. Keith Cannan, Hans T. Clarke, John T. Edsall, G. L. Foster, Stanford Moore, David Shemin, Esmond E. Snell, and Hubert B. Vickery. New York Academy of Sciences. 1946. pp. 239.

This little paper bound volume will be of great interest to biological chemists who are interested in the latest views in regard to the amino acids.

HYGIENE. Fourth Edition. By F. L. Meredith, M.D. The Blakiston Company, Philadelphia. 1946. pp. 838. Price \$4.00.

This is a textbook for college students on physical and mental health from personal and public aspects. Its popularity appears to be due largely to the fact that the material is well chosen and well written.

MEDICAL RESEARCH—A SYMPOSIUM—*Edited by Austin Smith, M.D.* with chapters by *Walter C. Alvarez, M.D., Milton G. Bohrod, M.D., Eldon M. Boyd, M.D., Herbert O. Calvery, Ph.D., S. deWitt Clough, Morris Fishbein, M.D., H. Lou Gibson, Torald Sollmann, M.D., and Austin Smith, M.D.*

This is an interesting and useful volume which many physicians will enjoy reading. There are chapters on the fundamentals of medical research, on some practical aspects of research, on the laboratory and the many types of work that are done in laboratories, on the manufacture and the development of new drugs, on medical research in the University Medical School, on the type of clinical research work that can be done by any physician with a notebook, on publicizing scientific research and on photography in medical research. Doctor Austin Smith is to be congratulated on carrying to completion this valuable work. The reproductions of medical illustrations, some of them in color, are beautiful.

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MOUTH AND ESOPHAGUS

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dog. *Proc. Soc. Exp. Biol. Med.*, 62: 140
(June) 1946.

Experiments on unanesthetized dogs are reported on the effect of distention of a segment of jejunum (Thiry fistula) upon tonus of the cardia and upon the relaxation of the cardia resulting from swallowing or from esophageal distention. The cardia is not easily influenced by changes in jejunal pressure. Repeated moderate distention of a short jejunal segment may produce a decrease in tonus of the cardia without nausea or distress. Distention of a jejunal segment does not alter the relaxation-contraction pattern of the cardia produced by the swallowing act or by esophageal distention.

H. NECHELES.

STOMACH

RESNICK, B. Diverticulum of the cardia
of the stomach. Report of three cases.
Am. J. Roent. Rad. Therapy, 55: 730
(June) 1946.

Three cases of diverticulum of the cardia of the stomach were encountered in 1,000 X-ray examinations. In these three cases the histories presented ulcer-like symptoms. There was epigastric pain; in two the onset of this pain occurred about one hour after eating. In the third case there was no relation to food ingestion. The symptoms improved under conservative treatment.

MAURICE FELDMAN.

FREEMAN, H. Duodenal ulceration: A gastroscopic study of the gastric mucosa and its surgical significance. *Brit. Med. J.*, 4460: 980 (June) 1946.

Gastroscopy was performed in 50 cases of duodenal ulceration. In 38 (76%) the

mucosa was interpreted as being hyperplastic. Many crowded, thickened, and extremely tortuous folds were observed, which persisted despite full inflation of the stomach. These folds were most marked along the posterior wall of the stomach. An associated superficial gastritis was present in 15 patients, a nodular gastritis in 7, and an antral gastritis in 2 cases. In patients with obstruction, viscid adherent secretion and a dulling or granularity of the mucosal surface were noted. These changes were more marked in the presence of chronic obstruction; in addition to being covered with excessive secretion, the folds were very edematous and segmented.

The author emphasizes the fact that the hyperplastic type of mucosa secretes increased quantities of acid gastric juice, and therefore is very liable to stomal ulceration after gastroenterostomy. The operative procedure of Somervell, in which a large proportion of the arteries supplying the stomach are ligated, is advocated. Gastroscopic examination of patients before and 6 months after gastric arterial ligation had been performed revealed that the mucosa in simple hyperplasia had undergone a marked transmutation from the hyperplastic state to one considered within normal limits.

JOSEPH B. KIRSNER.

MACKENZIE, W. C., MACLEOD, J. W., AND BOUCHARD, J. L. Trans-pyloric prolapse of redundant gastric mucosal folds. *Can. Med. Assoc. J.*, 54: 553 (June) 1946.

Two cases of transpyloric prolapse of redundant gastric mucosal folds, proved by operation, are described. The etiology of this condition is obscure. The condition may be due to a pre-existing gastritis or to an interference with the neuromuscular mechanism controlling the movements of the mucous membrane. There is no characteristic clinical syndrome. The most constant symptom is vague upper abdominal distress. The diagnosis is established by Roentgen examination. The X-ray appearance is variable, depending upon the degree of redundancy and prolapse. The polypoid appearance is probably the one most frequently encountered and is the

easiest to identify. The pyloric narrowing type is almost impossible of differentiation from numerous other conditions which may also diminish the calibre of the prepyloric region.

There is no specific medical treatment. Dietary and psychotherapeutic measures, tending to reduce mucosal engorgement and muscular hypertonus, are indicated theoretically. The positive indications for surgery are (a) equivocal Roentgen findings, when differentiation from polyps or other growths is not possible, (b) continued bleeding, and (c) evidence of pyloric obstruction, clinical or radiographic. Resection of the redundant and prolapsing fold, and closure by pyloroplasty, are advocated. The operation must include inspection of the interior of both stomach and duodenal bulb.

JOSEPH B. KIRSNER.

BOWEL

DIXON, C. F., LICHTMAN, A. L., WEBER, H. M., AND McDONALD, J. R. Malignant lesions of the duodenum. *Surg. Gyn. Obs.*, 83: 83 (July) 1946.

To date, 718 cases of malignant lesions of the duodenum have been reported, of which 433 are acceptable. The lesion is not as rare as textbooks state it to be. Roughly, it occurs about 33 times in 100,000 necropsies as compared with 3,000 times for carcinoma of the stomach. It comprises 0.3% of all intestinal carcinomas.

An analysis of 49 cases, exclusive of lesions of the papilla of Vater, is discussed in this article. In 3 of the cases diverticula were present, and in 1 case an aberrant pancreatic nodule was found. The lesions were seen to be quite evenly distributed throughout the duodenum. Obstructive features were prominent in 38 cases, while in 6 anemia resulting from loss of blood was the chief finding. The symptoms appeared to be a result of the morphologic characteristics of the lesion rather than of its position. Obstruction by a napkin ring stenosis or by intraluminal polypoid lesion is most common; next, the lesion may ulcerate or slough with production of bleeding. The third process to modify symptoms is a perforation into the pancreas, and fourth is obstruction of the biliary or pancreatic ducts.

Radical resection was done in 4 cases, segmental resection in 4, and local excision in 1. Operative mortality rate in cases in which procedures other than exploration were performed was 22%. Furthermore, it was concluded, carcinoma of the duodenum may originate from any of the cells mentioned, but the bulk of the lesions represent anaplastic changes in the duodenal mucosa itself.

FRANCIS D. MURPHY.

MORRISON, L. M. The control of diarrhea by tomato pomace. *Am. J. Dig. Dis.*, 13: 196 (June) 1946.

Tomato pomace was employed in the treatment of various types of diarrhea in a series of over 100 cases during a 5 year period. Diarrhea from simple or non-organic cause was usually arrested within 24 hours following treatment. For diarrheal medication, the author advises the use of tomato pomace.

H. J. SIMS.

DRUCKER, V. AND COHEN, E. S. Megaduodenum secondary to an intrinsic duodenal diaphragm. Report of a case. *Am. J. Roent. Rad. Therapy*, 55: 726 (June) 1946.

The authors report a case of megaduodenum due to a congenital duodenal diaphragm. This is the ninth recorded instance of this condition occurring in an adult (female aged 23 years). The patient gave a history of repeated projectile vomiting, which occurred once every two weeks from birth until the age of six years. At the age of three the patient ingested charcoal powder, which appeared in the vomitus three months later. X-ray examination made at the age of five revealed a stomach abnormality for which surgery was advised. Physical examination revealed a well-developed and well-nourished individual with a distended upper abdomen. A flat roentgenogram of the abdomen on admission revealed a distended stomach. A gastrointestinal study demonstrated an enlarged stomach with tremendous dilatation of the first and second portions of the duodenum. A constriction was noted in

the second portion of the duodenum. At operation, a diaphragm was found.

Congenital obstructions are attributed to the fact that the primitive gut closes solidly when the embryo reaches five weeks. This obliteration of the lumen is due to proliferation of epithelial cells. The lumen of the embryonic bowel is soon restored by the formation of vacuoles among the proliferated cells, and the coalescence of these vacuoles to complete recanalization. The faulty recession of these cells is said to give rise to stenosis, atresia, and congenital diaphragm.

MAURICE FELDMAN.

BENNETT, A. H. Crohn's disease—report of two cases. *Lancet*, 250: 846 (June) 1946.

The author reports two cases of Crohn's disease which were operated upon. In one case, short-circuiting the lesion by an ileo-colostomy was adequate. The lesions resolved completely and permanently, as proven by subsequent surgery five years later for metrorrhagia, and clinical follow-up two years subsequent to this last operation. In the second case, excision and ileo-colostomy were performed with apparently good results. The author stresses that his 2 patients were relatively early cases of Crohn's disease which had fortunately come to operation by reason of early obstructive phenomena. "Had they not been operated on at this stage, subsequent infection might have led to sinus formation and possibly peritonitis."

DAVID J. SANDWEISS.

HANES, W. J. Experiences in non-specific diarrheal conditions in the European Theater of Operations. *Am. J. Dig. Dis.*, 13: 199 (June) 1946.

This author made a clinical survey and investigation of diarrhea occurring in certain army units. Gastric analysis in normal and diarrheal states was likewise determined. The clinical findings were discussed as follows: (1) gastrogenic diarrhea, (2) persistent and recurring gastric diarrhea, and (3) persistent and recurring psychogenic diarrhea. Etiologic factors, effect of increased fat intake, and the

pharmacological action of dilute hydrochloric acid are discussed.

H. J. SIMS.

SMEDAL, M. I. The use of double contrast enemas in lesions of the colon. *Surg. Clinics N. Am.*, 594 (June) 1946.

The procedure should be used in all cases of suspected polyps, and in those in which polyps are demonstrated by proctoscopy and sigmoidoscopy, in order to determine the presence of additional polyps. Repeated examinations are desirable to avoid confusion with a fecal bolus and to ascertain the presence of polyps. It is of value mainly in left colonic examination, since overfilling results in poor visualization. The double contrast enema has been of value in a few cases in which a differential diagnosis between diverticulitis and malignancy is needed. Stereoscopic films aid in visualizing the mucosal pattern. The regular barium enema must precede the double contrast enema. Numerous excellent illustrations to substantiate its value are presented.

FRANK G. VAL DEZ.

SWINTON, N. W. AND GILLESPIE, J. L. The diagnosis of carcinoma of the colon and rectum. *Surg. Clinics N. Am.*, 553 (June) 1946.

The average time between onset of symptoms and actual operation for malignancy has been approximately 9 months. Symptoms are grouped under the following headings: (1) abnormality of the stool; (2) change in normal bowel habit; (3) unexplained abdominal pain, cramps, indigestion, or feeling of fullness; (4) an unexplained abdominal tumor or anemia.

Differential diagnosis of malignant disease from chronic stenosing regional enteritis, tuberculosis of the ileo-cecal region, diverticulosis, diverticulitis, spastic colon, polyps and polyposis, and ulcerative colitis is discussed.

To insure earlier diagnosis of cancer, digital examination and sigmoidoscopic examination should be a part of every complete general examination. In patients presenting any of the above symptoms, a careful and complete examination of the

rectum and colon should be undertaken; it should include a careful history and physical examination, digital examination of the rectum, proctoscopic and sigmoidoscopic examination, and radiographic studies of the colon.

FRANK G. VAL DEZ.

BOEHME, E. J., AND HANSON, P. J. Carcinoma of the colon and rectum: Site of growth of 1,457 lesions. *Surg. Clinics N. Am.*, 551 (June) 1946.

Seventy-five per cent of the malignancies of the large bowel are found in the sigmoid, rectosigmoid, and rectum. The remaining 25% of the lesions are almost equally distributed throughout the rest of the colon, except for the cecum which has slightly over 6% of the total.

Seventy per cent of the cancers of the colon can be palpated by digital examination, or can be seen through the sigmoidoscope. In addition to these, benign polyps and adenomas, which occur so frequently in the same region of the colon, can be found and removed.

FRANK G. VAL DEZ.

TRACEY, M. L. Roentgen diagnostic methods for detection of colonic lesions. *Surg. Clin. N. Am.*, 603 (June) 1946.

To determine the location and extent of colonic lesions above the rectum and sigmoid, roentgenography following the barium enema is the method of choice. Preparation is not advised since this may mask functional disturbances. If suspicious findings are encountered, repeating the procedure after proper preparation of the patient and air contrast films are in order, particularly where polyps are suspected. Findings in the cecum and ascending colon are very deceptive and may require the use of the Miller-Abbott or Rehfuss tube and a small amount of dilute barium to visualize these areas more readily and accurately.

FRANK G. VAL DEZ.

CARRUTHERS, L. B. Chronic diarrhea treated with folic acid. *Lancet*, 250: 849 (June) 1946.

The author reports 6 cases of chronic diar-

rhea of varied etiology, which showed rapid improvement in the character of the stools when treated with folic acid. Three of the cases had chronic amebiasis, one had bacillary dysentery, and the remaining 2 cases were of the idiopathic type. The patients with amebiasis did not respond to the usual anti-amebic therapy. Folic acid was given in 50 mg. doses daily for 5 days, followed by 15 mg. daily doses. Improvement in the character of stools was noted on the third day. The author suggests that in any long-standing diarrhea (regardless of etiology) a nutritional factor "prolongs the production of abnormal stools" and "folic acid appears to correct this defect. It is also probable that the need for folic acid persists, in view of the reversion to looseness where maintenance doses of the drug were not continued".

DAVID J. SANDWEISS.

LIVER AND GALL-BLADDER

GUYTON, W. L. Double gallbladder. *Am. J. Surg.*, 72: 118 (July) 1946.

Congenital anomalies of the gallbladder are uncommon. The literature reveals only 40 cases of congenital reduplication of the gallbladder, proven by autopsy or operation. This anomaly is divided into two groups: (1) vesico divisa or cleft gallbladder, the result of division of the primary cystic diverticulum forming a partial reduplication of the organ with 2 cavities emptying into a common cystic duct; (2) vesica duplex, composed of two gallbladders with two cystic ducts.

This is a case report of vesica divisa discovered during a cholecystectomy on a 42 year-old white woman and confirmed by pathological examination. Both cavities contained calculi, and on microscopic examination there was positive evidence of inflammation.

MICHAEL W. SHUTKIN.

LARGE, O. P., THORP, F. Q., AND KANE, S. Congenital atresia of the bile ducts. *Am. J. Surg.*, 72: 91 (July) 1946.

This report records 2 additional cases of atresia of the biliary ducts which recovered from operation, and illustrates some of the surgical features in the management of this

disease. The diagnosis is difficult and usually is proved only at operation or autopsy. The majority of patients found to be inoperable have died within 2 years, and autopsy has revealed no extrahepatic biliary ducts with marked cirrhosis of the liver.

The first case explored was a 12 day-old infant with atresia of the distal common duct; a successful cholecystogastrostomy was accomplished. The second infant at operation disclosed atresia of the cystic, hepatic, and common bile ducts; a small catheter was left along the inferior surface of the liver at the site of the common duct. Though the latter case was apparently inoperable, jaundice disappeared within 8 weeks, and at the end of one year the patient was living and well.

MICHAEL W. SHUTKIN.

HERBUT, P. A., AND WATSON, J. S. Metastatic cancer of the extrahepatic bile ducts producing jaundice. *Am. J. Clin. Path.*, 16: 365 (June) 1946.

Three instances of the metastatic infiltration by cancer cells of the extrahepatic bile ducts leading to obstructive jaundice are reported. The first case occurred in a 60 year-old white male in whom the primary lesion was an adenocarcinoma of the splenic flexure of the colon. Multiple papillomatous metastases were found in the mucosa of the common bile duct and the hepatic ducts, together with infiltration of cancer cells into the submucosa and between the muscle bundles. The tumor cells were similar to those of the primary growth. Deep jaundice and ascites had existed for 5 weeks prior to death. The bile ducts were dilated and sections of the liver showed advanced obstructive biliary cirrhosis.

The second case was that of a 13 year-old white boy in whom the primary lesion was a rapidly growing lymphosarcoma of the anterior mediastinum. All of the extrahepatic bile ducts were infiltrated with firm gray neoplastic tissue. The lumens of the ducts were almost completely closed, but the lining epithelium remained intact. The central portions of the liver lobules showed severe fatty changes, but cirrhosis had not yet occurred.

The third case was that of a 56 year-old white male who had been ill 6 weeks and died on the fifteenth postoperative day. The primary growth was a carcinoma of the descending colon. One of the metastatic nodules in the hilum of the liver was situated at the union of the left and right hepatic ducts. There was massive infiltration of the periductal connective tissue with cancer cells at this point with compression of the common duct and invasion of the adjoining portion of the liver. Scattered metastases and early biliary cirrhosis were found in liver sections.

The authors found no similar reports in recent medical literature of metastatic cancer invading the walls of the extrahepatic bile ducts and producing obstructive jaundice.

N. W. JONES.

WILSON, C., POLLOCK, M. R., AND HARRIS, A. D. Diet in the treatment of infective hepatitis. Therapeutic trial of cysteine and variation of fat content. *Lancet*, 250: 881 (June) 1946.

Five grams of d,l-cysteine were administered by mouth to 52 patients with infective hepatitis from the day of admission until the urine became bile-free by the foam test. Half of these patients were placed on a high fat diet of 200 g. per day, and the rest on a low fat diet of 70 g. The protein intake was the same at about 100 g. Fifty-one cases served as controls, divided evenly between the high and low fat diet regimen. The results showed that the cysteine-treated cases made a quicker recovery. There were, however, more relapses in the control group, and if these relapses are excluded, no significant difference can be observed between the cysteine-treated patients and the controls. It is possible that cysteine protects against relapse. The recovery rate of the patients on the high fat diet was the same as for the individuals placed on a low fat diet.

PHILIP LEVITSKY.

GLENN, F. The surgical treatment of acute cholecystitis. *Surg. Gyn. Obs.*, 83: 50 (July) 1946.

This article presents a definition of surgical

treatment of acute cholecystitis, and elaborates upon the operative procedures commonly employed. The indications and contraindications for each procedure are reviewed, and the resulting complications discussed. It was determined that surgical treatment of acute cholecystitis can be accomplished with a mortality rate comparable with that of nonacute biliary tract disease. Acute cholecystitis is more serious in those who are 50 years of age or older. Cholecystostomy can frequently be used in the seriously ill to tide them over an episode that would go on to irreversible complications, or in those who might not survive a more formidable surgical procedure such as cholecystectomy. Exploration of the common duct should be undertaken in the presence of acute cholecystitis only when there are clear-cut indications.

A policy that provides for the surgical treatment of acute cholecystitis and places the patient in a hospital should be to his best interest. Successful surgery is dependent upon every detail associated with it; preoperative and postoperative care and meticulous surgery are necessary to support this policy.

FRANCIS D. MURPHY.

FLICKINGER, F. M. AND MASSON, J. C. Reconstructive operations for benign stricture of the bile ducts. *Surg. Gyn. Obs.*, 83: 24 (July) 1946.

This article evaluates a series of reconstructive operations in 188 cases of benign stricture of the bile ducts. At least 12% of the strictures in this study were best explained on the basis of a low-grade chronic inflammation, so-called chronic obliterative cholangitis. It was concluded that surgical treatment does offer a real hope in certain types of stricture, as 55 to 62% of the patients made satisfactory recoveries after choledochoduodenostomy. If cholangitis and obstructive symptoms develop after a reconstructive operation, further surgical treatment should be deferred unless complete obstruction is definitely proved, as nearly half of the patients reported to be well 2 to 12 years after operation experienced transient cholangitis and symptoms of obstruction at one time.

However, surgical treatment should not be withheld on the grounds of poor risk; 188 patients underwent a total of 496 operations with only a 12% surgical mortality for the 188 procedures studied.

Progress has been made in the management of a complication that has arisen in the evolution of biliary surgery. The place that vitallium prosthesis will come to occupy remains to be ascertained, and the best treatment is still prevention. Surgeons must adhere to rigid care in actual identification of the structures they are handling when performing biliary operations.

FRANCIS D. MURPHY.

PANCREAS

DIXON, C. F., COMFORT, M. W., LICHTMAN, A. L., AND BENSON, R. E. Total pancreatectomy for carcinoma of the pancreas in a diabetic person. Metabolic studies. *Arch. Surg.*, 52: 619 (June) 1946.

Total pancreatectomy was performed on a 50 year-old diabetic man because of adenocarcinoma of the pancreas. His condition was good 12 months after operation. The following data were accumulated from an extensive follow-up study to show the effect of lack of internal and external pancreatic secretions.

Diarrhea did not occur in spite of the large amounts of fat in the stool, and bulkiness of the stools was reflected in abnormally high values for dry weight. Fat and protein accounted for most of this weight, since it was estimated that about half the ingested fat and one-third of the ingested protein was lost in the feces. Digestion of fat was surprisingly good, as only about one-third of that in the feces was neutral fat. The loss of food stuffs in the stool did not impair the absorption of calcium or phosphorus.

Concentrated pancreatin in enteric-coated tablets (15 with each meal, or 15 g. daily) reduced the loss of fat and protein by approximately 50%; it also reduced the dry weight and altered the gross appearance of the stool. Fat and nitrogen balance were not maintained by pancreatin, even in

excessive doses, but the latter was valuable in maintaining the nutrition of the patient.

Postoperatively, the patient's diabetes remained of about the same severity; he required about 40 units of protamine zinc insulin a day. It was interesting to note during 2 periods (89 hours each) of insulin privation, that the ketonemia was pronounced when 125 g. of carbohydrate was given and slight when 440 g. was given. Hepatic function remained unimpaired throughout, and hyperlipemia rather than hypolipemia appeared.

C. WILMER WIRTS, JR.

BARBOSA, J. DE C., DOCKERTY, M. B., AND WAUGH, J. M. Pancreatic heterotopia: Surgical cases. *Proc. Staff Meet. Mayo Clinic*, 21: 246 (June) 1946.

Pancreatic heterotopia is defined as being the presence of pancreatic tissue outside of its normal location and without any relation of continuity or of vascularization with the pancreas itself. In the present series of 41 cases, authenticated by microscopic examination, the anomaly was discovered at operation. The pancreatic dystopia caused symptoms in 61% of these cases. The most common location for such heterotopic tissue is in the stomach, duodenum, or jejunum, and it occurs three times more frequently in males than females. Warthin explained these structures as the result of the snaring-off and continued growth of epithelial buds of the pancreatic tissue as they penetrate the duodenal wall. Grossly and microscopically such heterotopic masses resemble normal pancreatic tissue. Histologic evidence of function was found in a high percentage of cases by means of special stain.

Hypoglycemia has been observed in some cases of dystopic islet-cell adenoma or adenocarcinoma. At exploration, in cases of hyperinsulinism where no tumor is found in the pancreas itself, aberrant pancreatic tissue should be searched for thoroughly. In the present series of cases exploration was done in many instances because of findings of gastro-duodenal disease, and extensive resections were performed in order to remove the lesion or because the benign nature of the mass was not recognized at

operation and carcinoma was the gross surgical diagnosis. No recurrence of symptoms was noted in any case following removal of the mass of dystopic pancreatic tissue.

FRANK NEUWELT.

ANEMIAS

RUNDLES, R. W. AND FALLS, H. F. Hereditary (sex-linked) anemia. *Am. J. Med. Sci.*, 211: 641 (June) 1946.

Familial hemolytic icterus, sickle cell anemia, and Mediterranean anemia are the best known inherited types of anemia. The authors investigated 2 families of non-Mediterranean origin in whom male members of several generations showed hypochromic anemia associated with abnormal erythrocytes and splenomegaly. The erythrocytes characteristically were irregularly shaped microcytes with varying hemoglobin concentration and no increase in fragility. Anemia was not found in any of the females, even though several of these transmitted the disease to their sons. The hematologic features of the patients available for study were similar to those with severe Mediterranean anemia. It is suggested that obscure hypochromic anemias which do not respond to iron therapy may represent inherited abnormalities of erythrocyte formation.

LEMUEL C. MCGEE.

KAUFMANN, J. AND SCHWAGER, P. G. Oral folic acid therapy in the treatment of pernicious (Addisonian) anaemia. *Can. Med. Assoc. J.*, 54: 539 (June) 1946. Four patients with pernicious anemia were treated with 20 to 40 mg. of folic acid daily, given in divided doses before meals. The synthetic preparation "Folvite" was used. Iron therapy was added when the blood became hypochromic; hydrochloric acid was permitted in one case. Within 3 or 4 days there was a marked feeling of well-being, and appetite and soreness of the tongue improved. Reticulocytosis was prompt, and maximum responses of 26 to 45% occurred on the fourth to ninth day of therapy. Red blood cells averaged a daily increase of approximately 90,000 per cmm., and showed an early return towards normal size and shape. Hemoglobin rose more

than 1% daily; the color index declined to less than 1, and the blood picture became hypochromic at times as the hemoglobinization lagged. The bone marrow, which prior to therapy showed a megaloblastic arrest of the red cell elements, rapidly became normoblastic in type. This was accompanied by an improvement in all the cellular elements, substantiated further by a return of the white blood count and platelet count to normal levels. Liver function impairment, evidenced by several tests, showed an early return to normal values.

The maintenance dose was arbitrarily placed at 5 to 15 mg. daily, but a smaller amount may suffice. No intolerance to the drug or allergic manifestations were noted. The authors feel that folic acid is not more effective than liver therapy in pernicious anemia but that it possesses certain advantages, namely, the simplicity of therapy with a lessened chance of complications and relapses, the shortened period of hospitalization, and the subsequent easier control of the disease.

JOSEPH B. KIRSNER.

ULCER

PRICE, P. B. The gastric digestion of living tissue. *Surg. Gyn. Obs.*, 83: 61 (July) 1946.

An experimental study was made to determine whether or not living tissues are susceptible to ordinary gastric digestion. Many different tissues (including omentum, intestine, gall bladder, liver, pancreas, spleen, kidney, lung, cartilage, skin, and gastric wall) were subjected to gastric digestion in healthy dogs. Testing was done by implanting living tissues and organs in the lumen of the stomach or by insuring prolonged surface contact with gastric secretion. Virtually all tissues so tested underwent digestion, which occurred in the absence of contributing factors of strangulation of the implant, infarction, infection, or autolysis.

Tissues most rapidly digested were external coats of hollow organs (intestines, appendix, gall bladder); those most resistant were fibrous connective tissue, skin, and intestinal mucosa. Only gastric epithelium seemed to be immune to ordinary digestion.

Organs and tissues projecting into the lumen of the stomach were much more rapidly and completely digested than were those placed tangentially in a gastric window.

Living tissues undergoing digestion showed different reactions. Serous surfaces became acutely inflamed, with rapid leucocytic infiltration and necrosis. Omentum and capsule of liver, spleen, and kidney responded with excessive amounts of fibrosis. Parenchyma of solid viscera presented complex pictures of fibrosis, hemorrhages, cellular infiltration, and necrosis. Some tissues tended to produce granulation tissue at the corroding surface. Epidermal surfaces slowly eroded with little or no cellular reaction. Once tissues are covered with proliferating gastric epithelium, they appear to be safe from further corrosive action of normal gastric juice.

FRANCIS D. MURPHY.

BARONOFKY, I. D., FRIESEN, S., SANCHEZ-PALOMERA, E., COLE, F., AND WANGENSTEEN, O. H. Vagotomy fails to protect against histamine-provoked ulcer. *Proc. Soc. Exp. Biol. Med.*, 62: 114 (June) 1946.

Supra- and infra-diaphragmatic vagus section was done in the dog, cat, and rabbit in order to find out whether it would protect against the ulcer provoked by histamine-in-beeswax.

Bilateral vagus section, as well as gastrojejunostomy and vagotomy, does not protect against ulcer or erosion (either gastric or duodenal) produced by chronic histamine stimulation. Bilateral vagus section alone may produce ulcers in the rabbit. Inasmuch as histamine acts directly on the parietal cell, the results of these experiments are not to be interpreted as a criticism of vagotomy for ulcer in man.

H. NECHELES.

BARONOFKY, I. D. AND WANGENSTEEN, O. H. Role of nitroglycerin in accelerating occurrence of histamine-provoked ulcer. *Proc. Soc. Exp. Biol. Med.*, 62: 127 (June) 1946.

Nitroglycerin dilates the smaller splanchnic vessels. Nitroglycerin-in-beeswax is shown to aid and abet the histamine-provoked

ulcer in dogs and rabbits. Venous spasm coupled with normal arteriolar reflex contractile responses leads, after prolonged administration of nitroglycerine, to impaired circulation in the mucous membrane of the esophagus, stomach and duodenum. These areas of lowered resistance are then subjected to acid-peptic digestion with resultant formation of either ulcer, erosion, or both.

H. NECHELES.

PROCTOLOGY

WILKINSON, S. A. Diagnostic significance of rectal bleeding. *Surg. Clinics N. Am.*, 574 (June) 1946.

Rectal bleeding is one of the most frequent of all complaints referable to the digestive tract. The cause of bleeding should not be left unexplained. Classification is conveniently based on location. In the anal canal, hemorrhoidal bleeding is the most common. Anal cryptitis, fissure, fistulas, and abscesses are uncommon sources of bleeding.

Rectal and sigmoidal conditions are classified as benign or malignant. Of the former, polyps are the most frequent; then ulcers, either amebic, tuberculous, bacillary, venereal or non-specific. Chronic ulcerative colitis and diverticulitis may also cause rectal bleeding.

Inspection and digital examination, as well as anoscopic and proctoscopic examination, are necessary and important parts of the investigation, and should never be omitted in any case of rectal bleeding. Radiographic examination should be done in all doubtful cases. If repetition of studies after careful dietary regulation does not disclose a cause, an exploratory laparotomy is not only justifiable but mandatory.

FRANK G. VAL DEZ.

BOEHME, E. J. AND CATTELL, R. B. Cancer of the rectum. A discussion of pre-operative preparation, postoperative complications and colostomy management. *Surg. Clinics N. Am.*, 564 (June) 1946. The pre-operative preparation of the patient is directed toward improvement of his general condition, and proper preparation and evacuation of the bowel itself.

There is much to be said in favor of tactfully avoiding any discussion of colostomy with the patient before surgery. All of the patients should understand that operation is imperative, that cure of the disease is the primary objective, and that what is to be done must be left to the judgment of the surgeon.

Colostomy bags or other apparatus, except a small gauze dressing or absorbent paper held in place with a 6"-wide elastic belt, are discouraged. The diet is so regulated as to favor constipation, and evacuations are accomplished with irrigations.

Post-operative complications are infrequent and consist mainly of pulmonary emboli or atelectasis, partial mechanical obstruction and obstruction with ileus, urinary retention and infection, thromboembolic disease, and wound infection.

FRANK G. VAL DEZ.

Ross, S. T. Ulcers about the anorectum.

N. Y. Stat J. Med., 46: 1339 (June) 1946. Ulcers may be classified as infective, physical, constitutional, toxic, and malignant. The symptoms are pain, discharge, and diarrhea usually of the before-breakfast variety. Ulcers having a purely local etiology are gonorrhoeal erosions, chancreoid (which is extremely rare above the anorectal line), lymphogranuloma venereum with stricture, follicular, stercoral, varicose, and hemorrhoidal. Ulceration may form part of a general constitutional disease, such as tuberculosis, syphilis, agranulocytic angina, and nephritis in the terminal stages. Bacillary dysentery, amebic dysentery, and chronic ulcerative colitis will affect the anorectum as part of a generalized colonic involvement. Factitial ulcers are due to irradiation of the uterus or other extrarectal structures. Trophic ulcers are extremely rare lesions, and are caused by disease of the lumbar segments of the spinal cord. Certain drugs, such as mercury and arsenic, if taken by mouth may give rise to toxic ulcers. Malignant ulcers are in a class by themselves, and in all suspected cases biopsy should be done.

The treatment should be constitutional where indicated. Certain specifics are

avored, such as sulfaguanidine in bacillary dysentery; emetine, carbarsone, and diodoquin in amebiasis. Local applications may be used in the form of argyrol 20%, silver nitrate 5%, and pure balsam of Peru. Bismuth subcarbonate or camphorated tincture of opium will control the diarrhea. Tenesmus may be relieved by the instillation of 2 ounces of warm olive oil.

PHILIP LEVITSKY.

SURGERY

KENNEDY, C. S. AND REYNOLDS, R. P.

Does anterior gastrojejunostomy predispose to development of jejunal ulceration? *Am. J. Surg.*, 72: 36 (July) 1946. This study was undertaken on 90 partial gastrectomies with a Polya type of anastomosis, to determine whether the anterior gastrojejunostomy predisposes to the development of a jejunal ulcer. A long loop of jejunum was brought anterior to the transverse colon, and the point of anastomosis was made 30-40 cm. from the ligament of Treitz. Gastric resection was performed distal to a line drawn between the left gastric artery and the avascular area on the greater curvature, thus removing all the acid-bearing area with the excitatory antral mucosa. Achlorhydria and the mechanical irritating effects upon the jejunal mucosa, both result post-operatively.

The follow-up failed to reveal a single instance of jejunal ulceration or enteroenterostomy. The mucosa of the jejunum in the long loop is able to withstand the direct contact of the gastric contents as well as the mucosa of the jejunum closer to the stomach. Anterior gastrojejunostomy does not predispose to the development of jejunal ulcer.

MICHAEL W. SHUTKIN.

BARBER, M. AND FRANKLIN, R. H. Bacteriology of stomach and duodenum in cases of peptic ulcer and gastric carcinoma.

Brit. Med. J., 4459: 951 (June) 1946. Swabs for bacteriological examination were taken directly from the mucosa of the stomach and duodenum at operation in 50 patients undergoing partial gastrectomy for peptic ulcer or gastric carcinoma. Bacteria were isolated from 16 of 40 cases of benign

ulcer, and from 9 of 10 cases of carcinoma. *M. albicans*, hemolytic streptococci, and coliform bacilli were isolated from patients who had a normal or high level of free hydrochloric acid. All other bacteria were isolated only from cases in which the test meal revealed an achlorhydria or a low concentration of free hydrochloric acid. Pyogenic cocci (*Str. pneumoniae*, *Staph. aureus*, and Lancefield A hemolytic streptococci) were isolated from 7 cases.

The authors point out that such organisms in the stomach at the time of operation are a potential source of infection. They suggest preoperative medication to eliminate bacteria from the stomach in those cases with low gastric acidity.

JOSEPH B. KIRSNER.

LAHEY, F. H. Selection of operation and technic of abdominoperineal resection for carcinoma of the rectum. *Surg. Clinics N. Am.*, 528 (June) 1946.

Complete abdomino-sacral removal of the lesions is the procedure of choice. It should be done preferably in one stage, but in approximately 15% a two-stage operation is necessary. Procedures concerned with the preservation of the sphincter are emphatically discouraged. The lesions are not considered inoperable if only a limited number of metastases within the liver exist, or if carcinoma of the rectosigmoid which has involved the uterus by contact alone is present, or if low carcinoma of the rectum directly over the prostate in which central excavation into one or both lobes of the prostate has occurred, or if lesions are adherent to the bladder providing there are no cystoscopic findings of bladder invasion. One convincing feature of inoperability in carcinoma of the rectum is fixation, particularly to the lateral walls.

Fractional spinal anesthesia has been utilized because of its unlimited time element, but also because of the satisfaction, the relaxation, and the quietness which it provides. The technical aspects of the operative procedure are thoroughly discussed. For the posterior portion, the left lateral position is chosen because of its greater facility of exposure and minimal interference with diaphragmatic respiratory

excursions. Massive gauze-packing of the pelvic cavity is discouraged.

The mortality in the past 4 years has been 3.8%, with an operability rate of 83% and a 5-year non-recurrence rate of 50%.

FRANK G. VAL DEZ.

CATTELL, R. B. AND COLCOCK, B. P. Primary resection of the right colon. *Surg. Clinics N. Am.*, 606 (June) 1946.

Primary resection is more desirable because (1) it is the simplest technical procedure for the surgeon, (2) it is more advantageous to the patient from the standpoint of both comfort and economic reasons, and (3) it has given good results from the standpoint of mortality and 5-year survival figures.

Better preparation and increasing surgical experience with these cases have increased the safety of primary resection. During 1945, 84 patients with cancer of the colon were operated on. Seventy-seven had resections, of which 62 had the modified Mikulicz procedure in 2 stages; 2 had a two-stage resection consisting of preliminary anastomosis followed by resection; and 13 primary resections of the right colon were performed. There was no operative mortality following primary resection.

FRANK G. VAL DEZ.

PHYSIOLOGY: SECRETION

THOMAS, J. E. AND CRIDER, J. O. The secretion of pancreatic juice in the presence of atropine or hyoscyamine in chronic fistula dogs. *J. Pharmacol. Exp. Therap.*, 87: 81 (June) 1946.

Doses of atropine or hyoscyamine sufficient to block the secretory endings of the vagus nerves decreased the specific gravity and total nitrogen of the pancreatic juice in unanesthetized dogs regardless of the stimulus used to promote secretion. When the stimulus was soap or HCl in the intestine, or intravenous secretin, the volume of the secretion was also decreased by the action of these drugs. The response to secretin was affected least. The volume of pancreatic juice obtained in response to peptone in the intestine was increased by atropine or hyoscyamine in 7 of 10 normal dogs. The secretory response of the pan-

creas which normally follows injection of peptone into a Thiry loop of the duodenum or jejunum was abolished by atropine or hyoscyamine. Either the parasympathetic innervation or some other mechanism that is affected by the parasympathetic depressants contributes to the secretion of enzymes by the pancreas in response to a variety of stimuli, including HCl and secretin.

ARTHUR E. MEYER.

PHARMACOLOGY

WINNEK, P. S. An intestinal antiseptic: 2-sulfanilamido-5-carboxythiazole. *Science*, 103: 719 (June) 1946.

2-sulfanilamido-5-carboxythiazole is poorly absorbed from the gastrointestinal tract and possesses high antibacterial activity. Any of the drug which is absorbed and partially acetylated will be freely soluble in the body fluids. This suggests strongly that there is little danger of deposition of crystals in the urinary tract.

In vitro experiments showed that 2-sulfanilamido-5-carboxythiazole possessed as much activity against streptococcus as did sulfanilamide, sulfadiazine, and sulfaguanidine. It showed appreciable activity against the enteric group of organisms, being in general more active than sulfanilamide and sulfaguanidine, and in some instances equal to sulfapyridine, sulfathiazole, and sulfadiazine. It was also strongly active against pneumococcus and staphylococcus.

This drug was found in experiments on mice to have much less chronic toxicity than sulfaguanidine, and was comparable with succinylsulfathiazole. It caused a marked reduction in the number of coli organisms in the feces of dog and man. Extensive clinical trials are now in progress to determine its value as an intestinal antiseptic.

CHARLES A. FLOOD.

MISCELLANEOUS

BRODIE, J., COOK, R. P., DRYSDALE, C. F., AND MCINTOSH, D. G. Treatment of Sonne III bacillary dysentery and bacillary dysentery ("clinical") with phthalyl

sulphathiazole. *Brit. Med. J.*, 4459: 948 (June) 1946.

The results of treatment of 48 cases of Sonne III dysentery and 40 cases of bacillary dysentery, diagnosed on the basis of the clinical manifestations, with phthalyl sulfathiazole are reported. The average periods required for the establishment of clinical cure were 8.73 days for the Sonne III cases and 9.83 days for the "clinical" group. Clinical relapse occurred in 25 of the 48 Sonne III cases, and in 20 of the 40 clinical cases. Seven (28%) of the 25 patients who relapsed yielded a positive bacteriological result during convalescence, as compared with 3 (13%) of 23 cases which did not relapse. Ten (20.8%) of the 48 Sonne III patients treated with phthalyl sulfathiazole gave a positive bacteriological result in convalescence.

Analyses of the feces, urine, and blood indicated that saturation of the contents of the bowel was achieved and that a small but definite absorption of the drug occurred. No toxic effects were observed in the 88 cases treated. In vitro experiments demonstrated that phthalyl sulfathiazole exerted a bacteriostatic effect against a Flexner strain, a Sonne III organism, and a strain of *B. coli*. The authors concluded that, while phthalyl sulphathiazole did not appreciably influence the clinical course of Sonne III dysentery, it reduced considerably the number of cases bacteriologically positive during convalescence.

JOSEPH B. KIRSNER.

TALLANT, E. J. AND MAISEL, A. L. Amebiasis among the American armed forces in the Middle East. *Arch. Int. Med.*, 77: 597 (June) 1946.

The authors describe their experience with amebiasis in an American army hospital stationed in the Middle East from November 1942 to November 1944. A single examination of native food handlers suggested that the incidence of *E. histolytica* was over 50%. Monthly examinations of purged stools from mess personnel in the hospital revealed that 36% acquired infection with *E. histolytica* during the two year period. Of all the patients admitted

to the hospital, 464 were infected; 26% were carriers; 36% had mild symptoms, 25% moderate, and 13% severe symptoms. These included abdominal pain and tenderness, temperature elevation, and diarrhea with periodic constipation.

The preferred plan of treatment included single daily intramuscular administration of 0.06 g. emetine hydrochloride for 6 days, with concurrent oral administration of 0.25 g. of carbarsone 3 times a day for 7 days. Following this, 0.6 g. of diodoquin was given orally 3 times a day for another 7 days. Less than 3% of those treated by this plan responded unsatisfactorily.

EDGAR WAYBURN.

KIEFER, E. D. The clinical significance of diarrhea. *Surg. Clinics N. Am.*, 579 (June) 1946.

The diarrheas may be classified as acute (enterocolitis, intestinal "flu," "summer diarrhea," and food poisoning), functional (caused by irritating food or drink, food idiosyncrasies, laxative drugs, nervous factors, achlorhydria, and irritable colon), and chronic organic diseases (such as cancer, benign tumors, polyposis, diverticulitis, tuberculosis, ulcerative colitis, bacillary dysentery, amebiasis, ileitis, sprue and other diseases of the small and large intestine).

While the two former groups require only symptomatic therapy, the third group requires early recognition and prompt therapy. Any case of diarrhea presenting the following features deserves a full diagnostic study: (a) a duration of more than 3 weeks, (b) the diarrhea represents a distinct change from the previous bowel habits, (c) the patient's age is over 40, (d) blood or pus in the stool, (e) persistent fever for more than a week, (f) signs of partial or intermittent intestinal obstruction,

(g) malnutrition and (h) anemia. Diagnosis should include a general physical examination, digital examination of the rectum, proctoscopy, roentgenologic study of the gastro-intestinal tract, microscopic examination and culture of the stool, tests for free HCl in the gastric juice, and routine blood counts and hemoglobin.

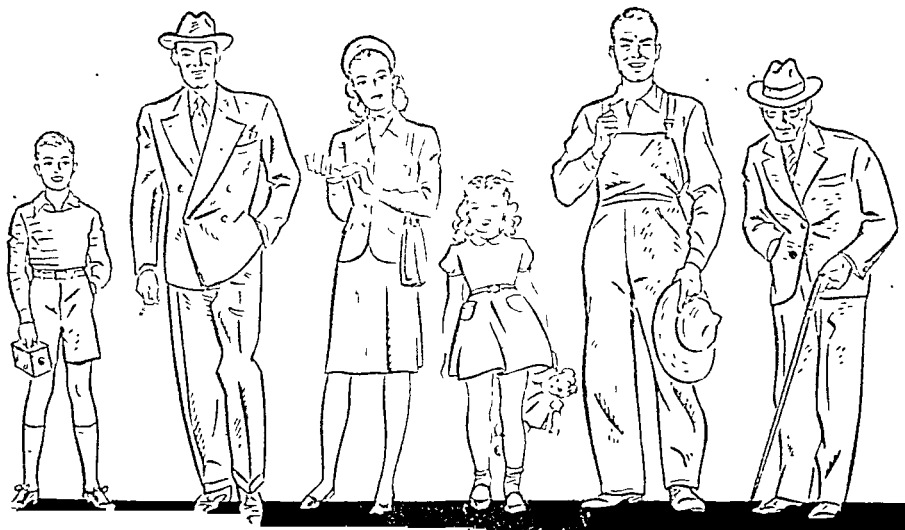
Descriptions of some of the important diseases which cause diarrhea have been included, along with brief outlines of the diagnosis and treatment.

FRANK G. VAL DEZ.

ROTH, L. W., RICHARDS, R. K., AND STEGERDA, F. R. Influence of various pharmacologic substances on the emetic effect of intravenous glutamic acid in dogs. *Proc. Soc. Exp. Biol. Med.*, 62: 284 (June) 1946.

With intravenous administration of amino acid mixtures and protein digests, nausea and vomiting occur often, particularly when the solutions are administered too rapidly. Glutamic acid and aspartic acid are held responsible for this effect. An attempt has been made to find drugs which will delay or inhibit emesis resulting from the infusion of a pure solution of the natural glutamic acid. Atropine, d-desoxyephedrine, tridione, or pyridoxine with thiamine, had no significant effect in delaying vomiting. Nembutal (2 mg./kg.) given intravenously 10 minutes before the glutamic acid infusion produced an 84% improvement in tolerance. Epinephrine, infused with glutamic acid in a concentration of 2 μ g./kg./min., produced a 45% tolerance increase. Tolerance to glutamic acid increased if infusions were repeated within 4 to 6 days.

H. NACHELES.



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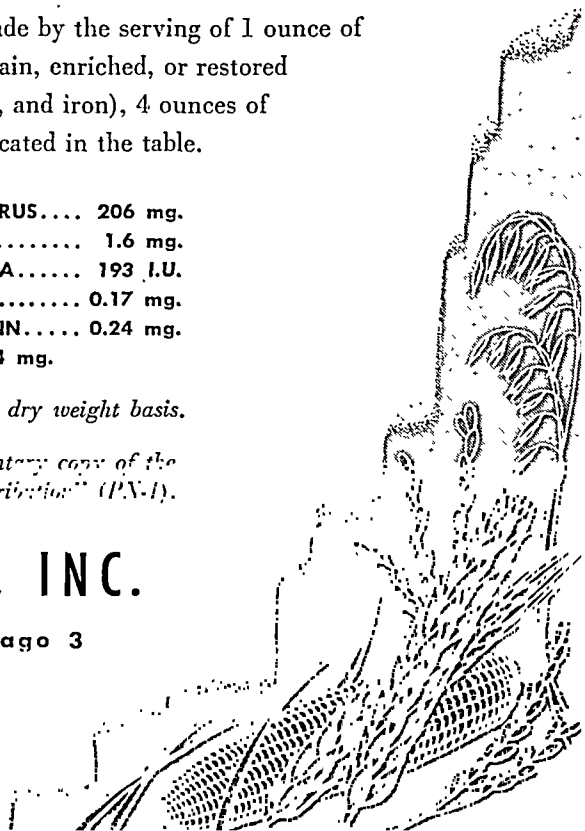
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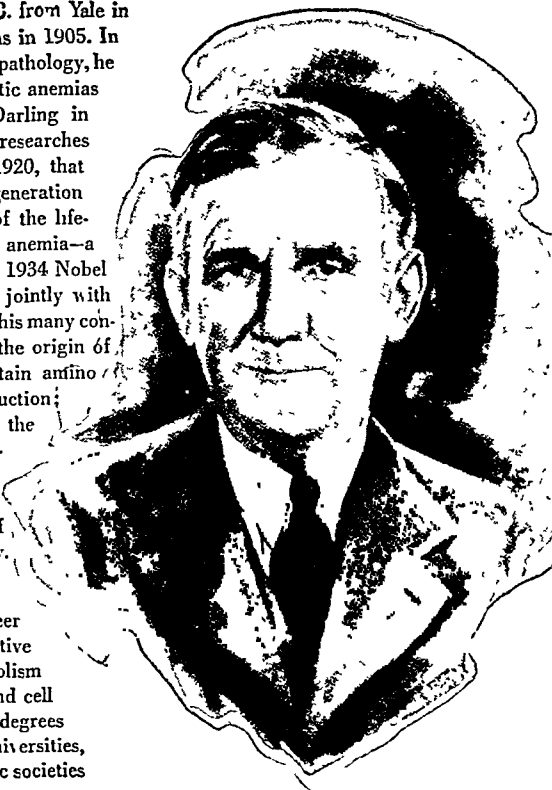
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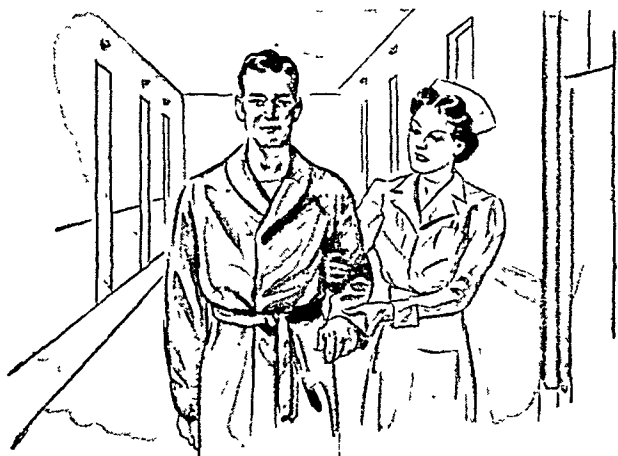
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ANNOUNCEMENT

Information Regarding Post-Graduate Instruction in Gastroenterology

At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

Those who are interested in obtaining such instruction should write promptly to the person or school of their choice; because in most instances the number of students who can be accommodated is limited.

Name	Place
Watson, C. J.	University of Minnesota
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Palmer, Walter L.	University of Chicago
Crohn, Burrill B.	New York
Benedict, Edward B.	Harvard Medical School
Perry, Thomas M.	Georgetown Univ., Wash., D. C.
Bockus, Henry L.	Univ. of Pennsylvania
Gray, Irving	Brooklyn
Rehfuess, Martin E.	Jefferson Med. College
Ivy, A. C.	University of Illinois
Ruffin, Julian M.	Duke University
Willard, John H.	Abingdon Memorial, Rochester, N. Y.
Moser, Rollin H.	Indianapolis
McCann, Wm. S.	Strong Memorial, Greenville, Pa.
Twiss, J. R.	Post Grad. Med. School, New York
Miller, T. Guier	Univ. of Pennsylvania
Atkinson, Arthur	Passavant Hospital, Chicago

Name	Place
Mateer, John G.	Henry Ford Hospital, Detroit
Hollander, Franklin	Mount Sinai Hospital, New York
Menkins, J. C.	Royal Victoria Hospital, Montreal
Crandall, L. A.	University of Tennessee
Wilkinson, S. Allen	Lahey Clinic, Boston
Carey, James B.	The Nicollet Clinic, Minneapolis
Patterson, Cecil O.	Dallas, Texas
Wood, W. Barry	Washington Univ., St. Louis
Sydenstricker, V. P.	University of Georgia
Laing, Grant H.	Chicago
Neches, H.	Michael Reese Hospital, Chicago
Garbat, A. L.	Lenox Hill Hospital, N. Y.
Rafsky, H. A.	Lenox Hill Hospital, N. Y.
Kantor, John L.	Montefiore Hospital, N. Y.
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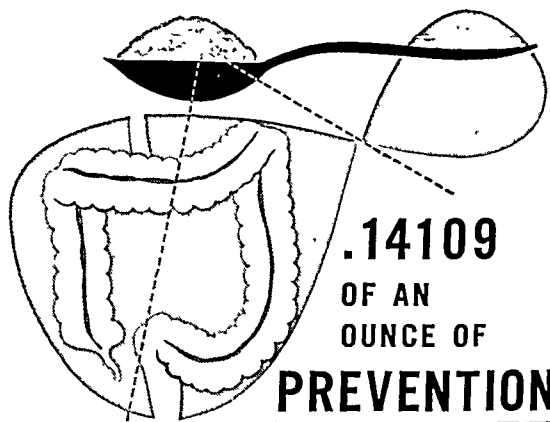
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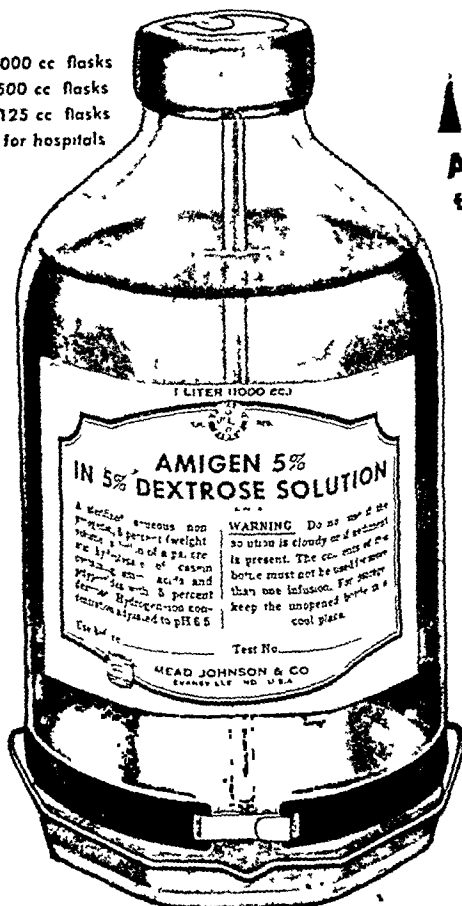
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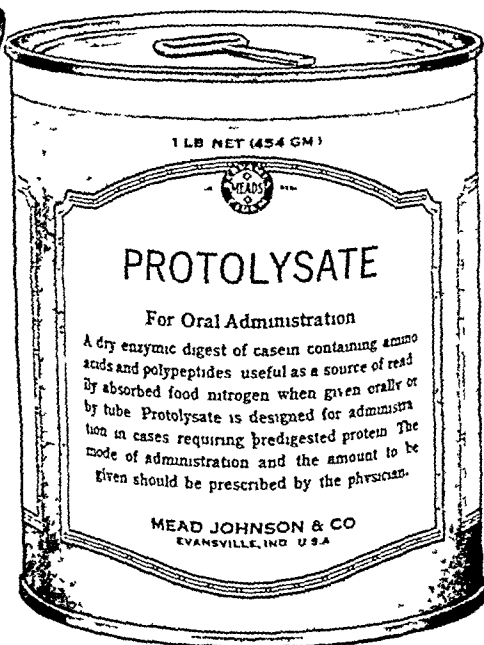
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APRIL, 1947

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Official Journal of the American Gastroenterological Association

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BARIUM

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*Waldapfel, R.: Pharyngoesophageal diverticulum, *Eye, Ear, Nose & Throat Month.*, 24: 579 (Dec.) 1945.



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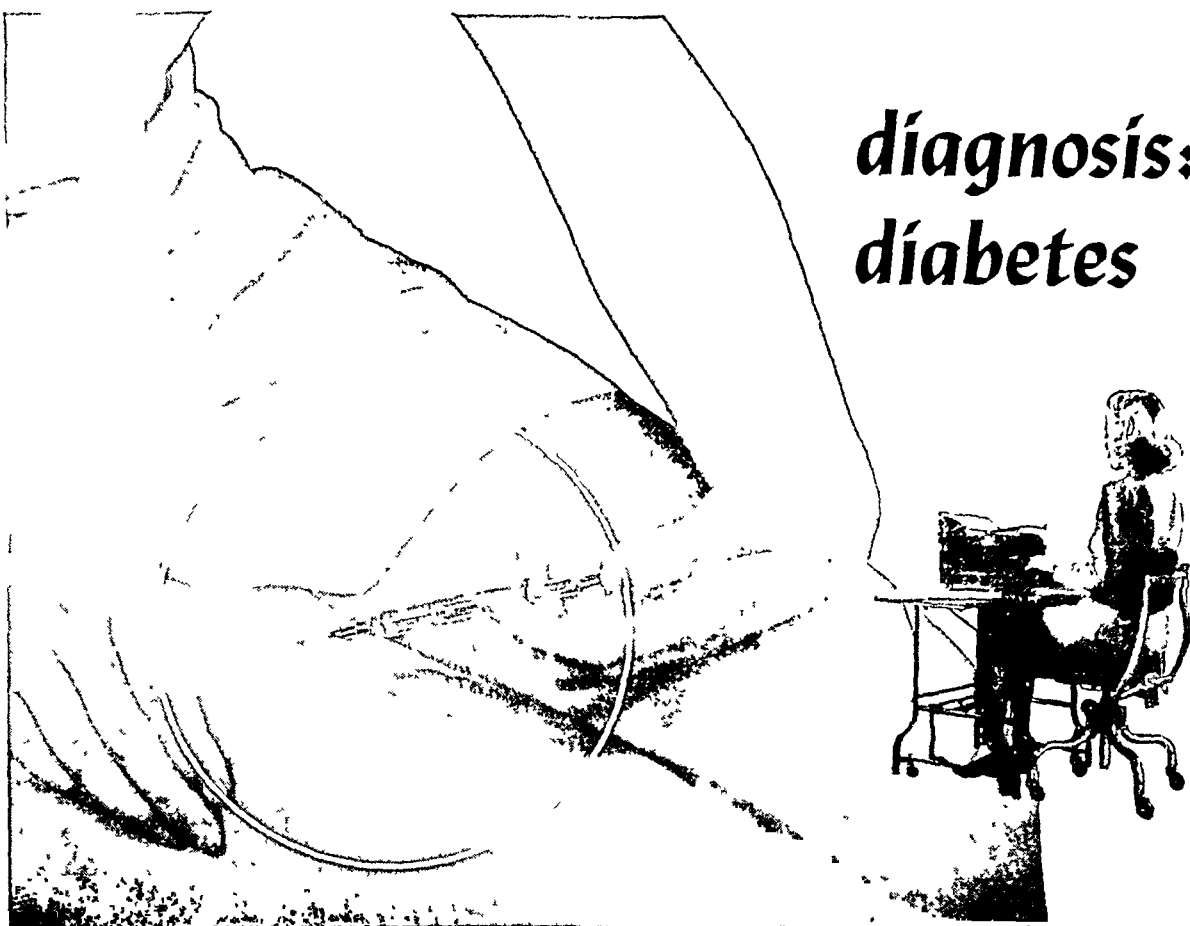
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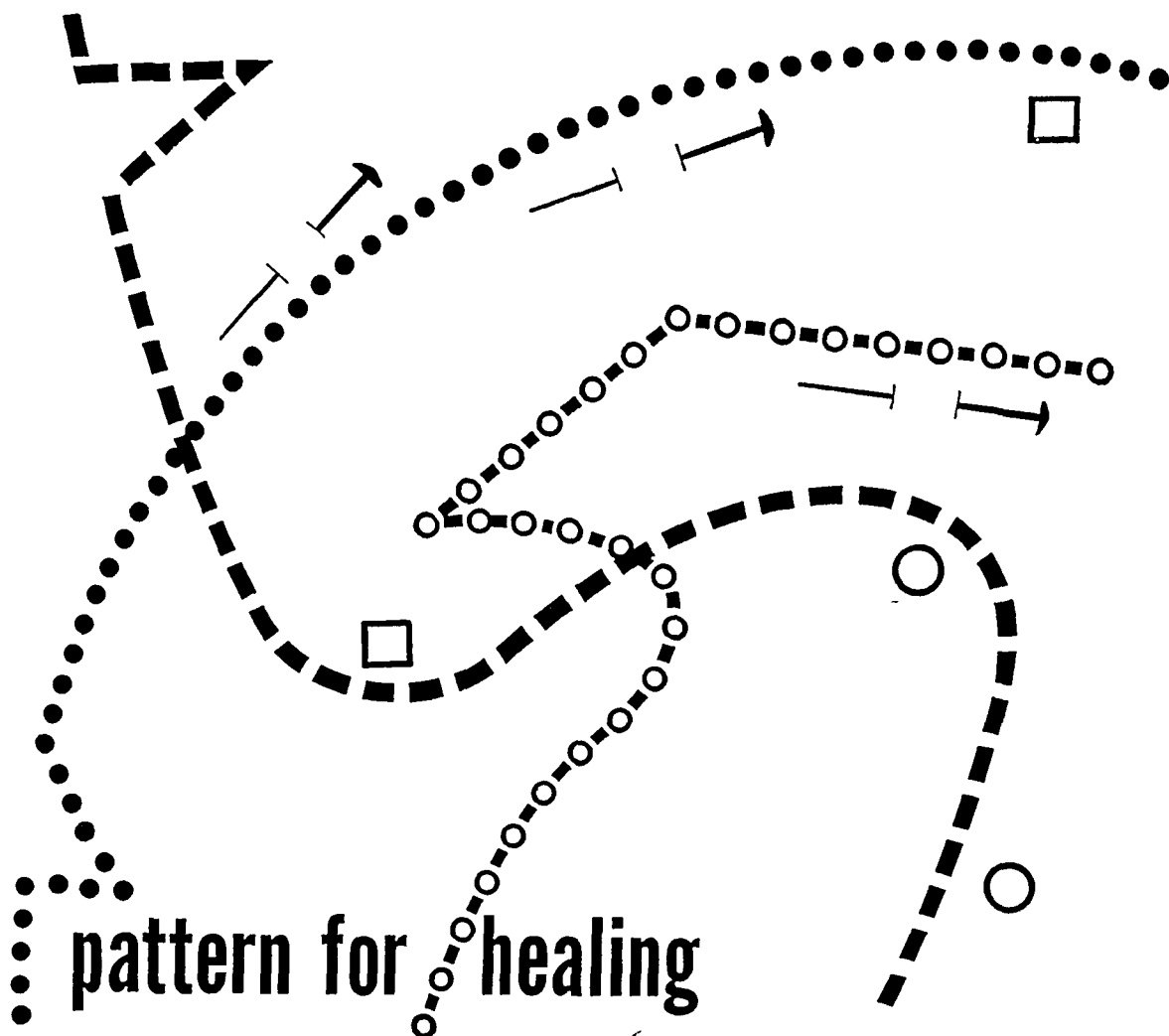


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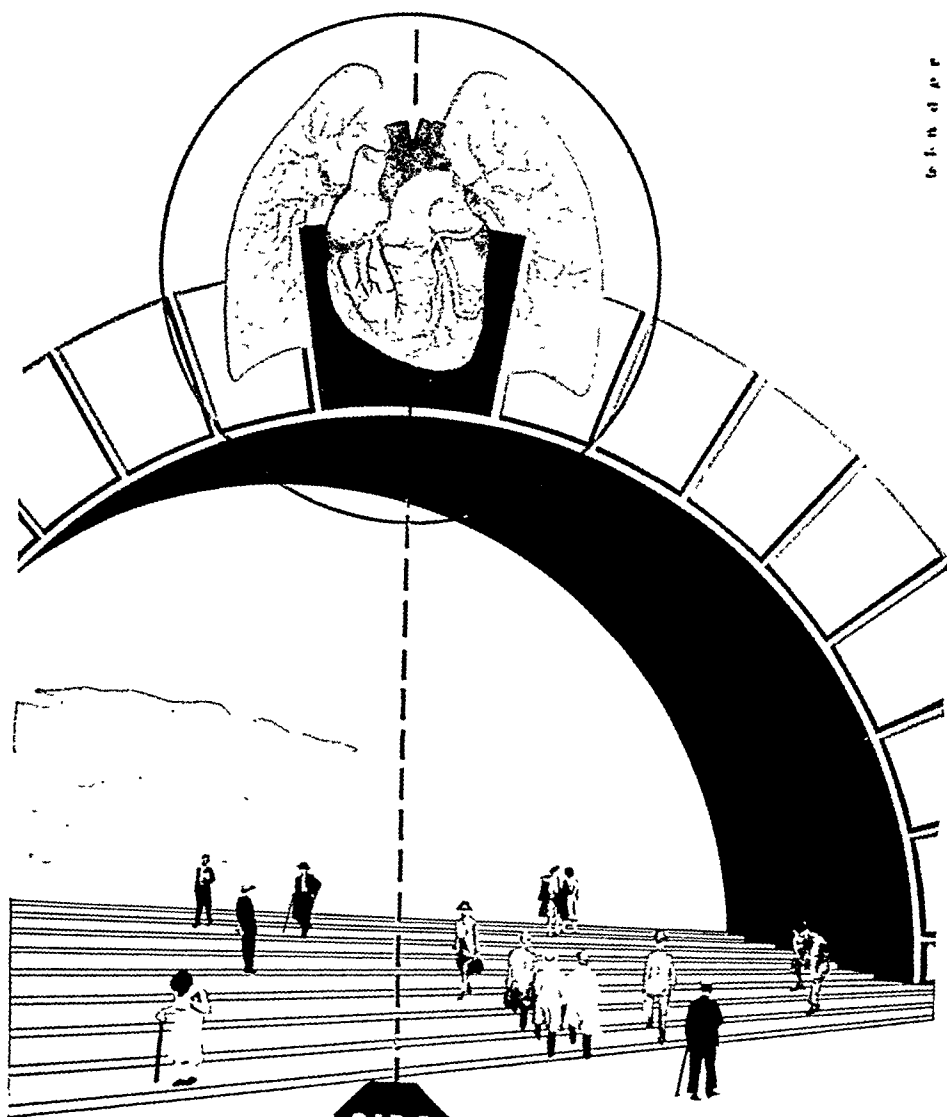
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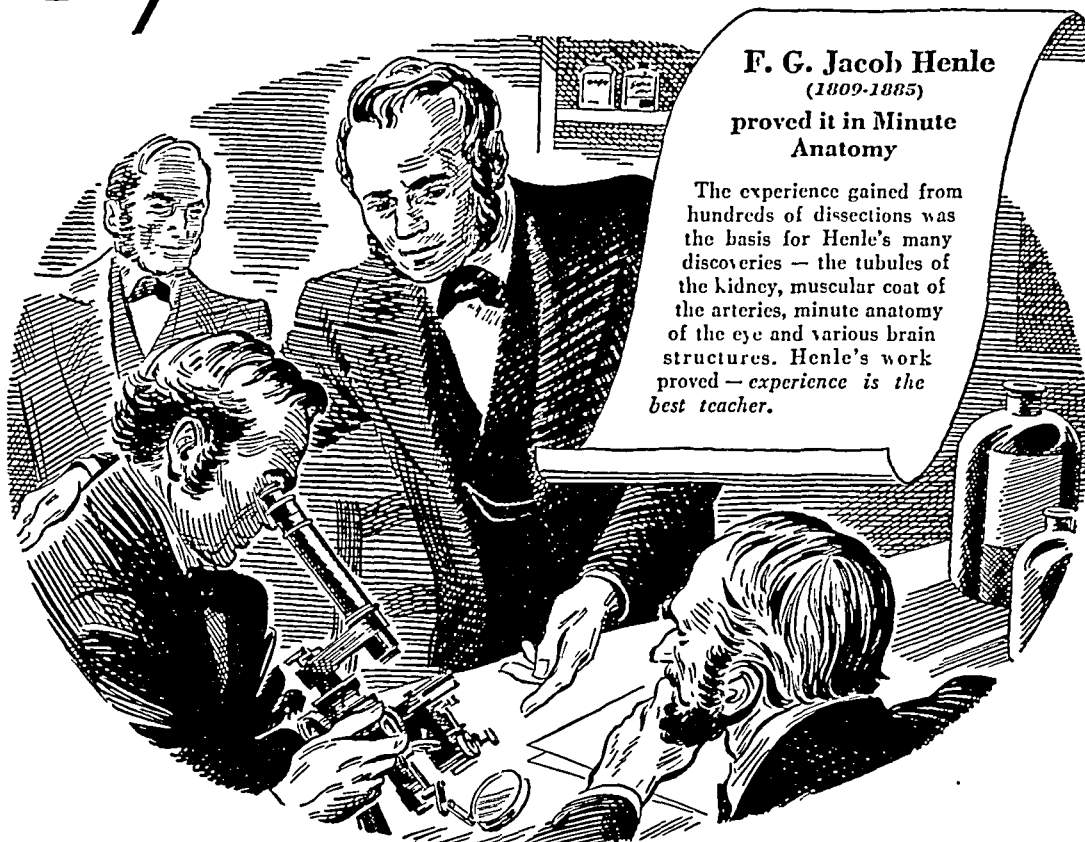
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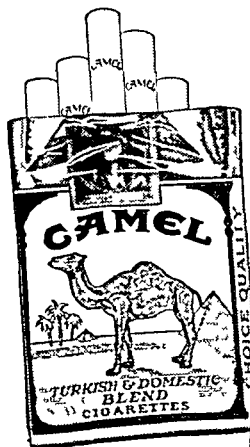


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GIANT HYPERTROPHIC GASTRITIS

SAMUEL N. MAIMON, M.D., JAY P. BARTLETT, M.D., ELEANOR M. HUMPHREYS, M.D., AND
WALTER LINCOLN PALMER, M.D.

*From the Frank Billings Medical Clinic, Departments of Medicine, Surgery and Pathology,
University of Chicago*

INTRODUCTION

Giant hypertrophic gastritis is a rather rare pathologic condition characterized by the presence of widespread and marked enlargement of the gastric folds. It assumes clinical importance primarily because of the difficulty in the differentiation from malignant lesions and secondarily because of the possibility that it may be a pre-malignant proliferation of the gastric mucosa.

The purpose of this paper is to describe 6 cases and to discuss the clinical and pathologic features of the entity.

INCIDENCE

A review of 5765 gastroscopic examinations carried out at this institution revealed the 6 surgically verified cases of diffuse involvement of this group while 4 others were diagnosed on the basis of x-ray and gastroscopic findings, two being confirmed by operation—an incidence of 0.17%.¹

The rarity of the "condition" is further illustrated by the fact that Balfour (1) in 8000 gastric operations encountered only one case, Carman in 50,000 x-ray examinations of the stomach found two; Eliason and Wright (2) discovered one in 8000 autopsies. In 1928, Strauss Meyer and Bloom (3) in reporting two cases stated that the total number recorded in the literature including their own was seven. Kantor (4) observed giant hypertrophic gastritis twice in 2,500 x-ray examinations while Feldman (5) in 25,000 such examinations found it once, the lesser curvature being involved. In 4,424 gastric roentgen examinations over a period of 18½ years Sprigg (6) noted 19 instances of giant hypertrophic or tumoral gastritis 7 of which were associated with gastroenterostomy or peptic ulceration. Schindler (7) reports three cases observed gastroscopically.

ETIOLOGY

The cause is unknown although many hypotheses have been postulated such as congenital anomalies, the effect of chemical, thermal and mechanical irritants, and the role of infectious agents.

¹ The incidence given is approximate, as it is based on the total number of gastroscopies rather than the number of patients encountered

CLINICAL PICTURE

It is difficult to know whether giant hypertrophic gastritis produces a typical clinical syndrome or, indeed, whether of itself it produces any symptoms at all. The existence of abdominal distress in such patients does not constitute evidence of a causal relationship. The demonstration of a pattern of pain or of other symptoms common to all cases would be suggestive. One of the six patients to be described gave a history of epigastric distress of ten years relieved by alkalis and diet; a second had noted a vague hollow burning upper abdominal ache for six months, not relieved by alkali; a third complained of gnawing epigastric discomfort relieved by food, and a sensation of upper abdominal fullness alleviated by eructation; a fourth patient had noted bloating and epigastric distress several hours after meals for one year and gave a history of a severe upper gastro-intestinal hemorrhage two years before the present episode with relief of the symptoms by milk and alkali; a fifth had intermittent epigastric distress for 35 years, occurring 30 minutes after meals, and relieved by refraining from food; a sixth displayed symptoms similar to those of the fifth. Thus, the outstanding features of all the cases were upper abdominal distress somewhat ulcer-like in character but not always relieved by food, alkalis or eructation and of extremely variable duration. It should be noted that in addition to the gastritis the second patient had a duodenal ulcer which may have accounted for the distress. Several previous authors have commented on the similarity of the distress to that seen in peptic ulcer; others have described only vague distress not following a definite pattern. Sprigg (6) found that epigastric distress and eructation were the predominating symptoms in seven cases, nausea in five, vomiting, weakness and headache in four, diarrhea in three and constipation in three.

Vomiting was prominent in two of our patients (Cases 2 and 5), prolapse of the mucosa through the pylorus being considered the probable mechanism. Eckhoff (8) has demonstrated, at operation, acute pyloric obstruction with partial intussusception of the stomach into the duodenum as the result of a giant or redundant hypertrophic gastric mucosa; Cole (9), indeed, states that pyloric obstruction is not uncommon in this entity.

Physical examination was normal in all the patients except two with some epigastric tenderness and peripheral edema, not disappearing with bed rest, a total plasma protein of only 4.9 gm. per cent and an A/G ratio of 1.74 in Case 2.

The age of the patients ranged from 33 to 71 years, four being under 46. The sex distribution was not remarkable but the occurrence of the 2 cases of polyposis in females is perhaps noteworthy.

The maximum gastric free acidity (histamine stimulation) ranged from 106

to 0. In Case 1 with a maximum histamine free acidity of 40, in Case 2 with a free acidity of 106 and in Case 6 with free acid present although the amount was not recorded, histologic study of the mucosal structure showed little alteration of the glandular elements. In Case 3 with a free acidity of 20 units and Case 4 with 10 units, histologic study revealed a progressive and marked increase in the replacement of the acid and pepsin forming cells by an intestinal type of goblet cells. Case 5 with histologic changes similar to Cases 3 and 4 plus a superimposed hyperplastic polyposis secreted no free acid at all in response to histamine. Thus in general the secretory capacity of the mucosa corresponded roughly with histologic appearance of the glands. Cox and Barnes (10) have shown that in the rat the gastric secretory capacity is related directly to the number of parietal cells present. Gill (11) reports that gastric secretion increases as the thickness of the mucosa, as seen gastroscopically, increases. Our studies are in accord with these observations. Parenthetically it should be noted, as will be shown later, that a grossly redundant and apparently hypertrophic mucosa may be found on microscopic examination to contain atrophic intestinal epithelium rather than the normal gastric glands.

The hemoglobin and red blood cell values were within normal limits in 5 of the cases; in Case 6 with polyposis slight anemia with an erythrocyte value of 3.76 was present. In the group reported by Freedman et al (12) four patients had anemia and weight loss as the outstanding finding.

ROENTGENOLOGIC MANIFESTATIONS

The rugae in Case 1 (Fig. 1) were extremely prominent, especially along the mid-portion of the greater curvature; the pliability of the folds, which could not be obliterated on pressure suggested gastritis rather than neoplasm. Two months later, repeated roentgen studies disclosed the same findings and 19 months later the gross irregularity without stiffness of the gastric wall was again noted. In a fourth examination, shortly after the third, a rounded defect appeared, protruding into the posterior wall just above the level of the angulus; the rugae of the upper stomach seemed completely destroyed and replaced by a large polypoid mass. Operation, however, revealed large papillomatous folds of giant hypertrophic gastritis in a redundant mucosa.

In Case 2 (Fig. 2) an extensive irregular defect along the greater curvature was attributed to a soft polypoid carcinoma rather than edema, although the softness of the folds was noted. Repeated roentgenologic study, 10 days later revealed, in addition to the previous findings, a deformity of the duodenal bulb compatible with ulcer. The softness and widespread distribution of the enlarged gastric folds was considered compatible with marked hypertrophic gastritis rather than neoplasm. Laparotomy confirmed the diagnosis of duodenal ulcer with hypertrophic gastritis.

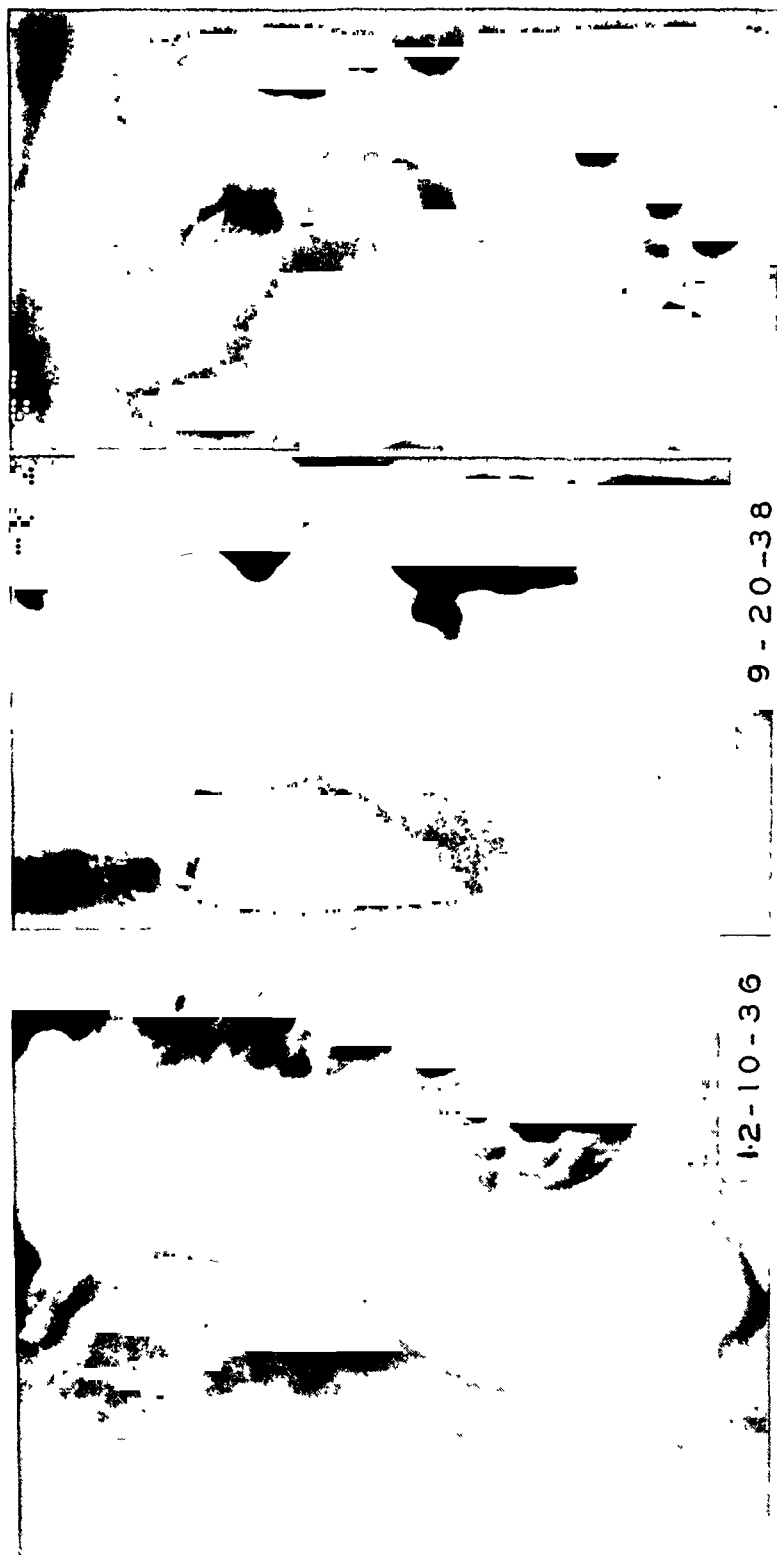


FIG. 1. Case 1. 12-10-36. (a) (Left.) Prominent pliable rugae of the greater curvature. 9-20-38. (b) (Center.) Disappearance of the rugae; gross irregular deformity of greater curvature suggestive of neoplastic infiltration. (c) (Right.) Oval defect near cardia suggestive of a large polypoid mass; ragged deformity of the greater curvature.

In Case 3 (Fig. 3) a completely irregular polypoid protrusion of the body of the stomach with stiffening of the posterior wall was noted, no ulcer crater



FIG. 2 Case 2 (a) (Left) Apical deformity of the duodenal bulb (b, center, and c, right) Irregular soft filling defect, more marked along the greater curvature.



FIG. 3. CASE 3 COMPLETELY IRREGULAR POLYPOID DEFECT OF THE BODY OF THE STOMACH WITH STIFFENING OF THE POSTERIOR WALL

was seen. Constant collections of barium between the elevations of mucosa gave the impression of multiple polyps, almost certainly polypoid carcinoma. The stiffness of the posterior wall favored the impression of neoplasm. Kantor

(4) in commenting on the difficulty in differentiating giant hypertrophic gastritis from carcinoma, has pointed out that sometimes a stiffening of the gastric wall may accompany the gastritis. Surgery proved such a condition to be present in this instance.

In Case 4 (Fig. 4) the rugal pattern was diffusely distorted with spectacular narrowing of the mid-portion of the stomach. Instead of the stiffness usually present in carcinoma the walls appeared soft and pliable. A soft infiltrating carcinoma involving the entire stomach was suspected but subsequent autopsy

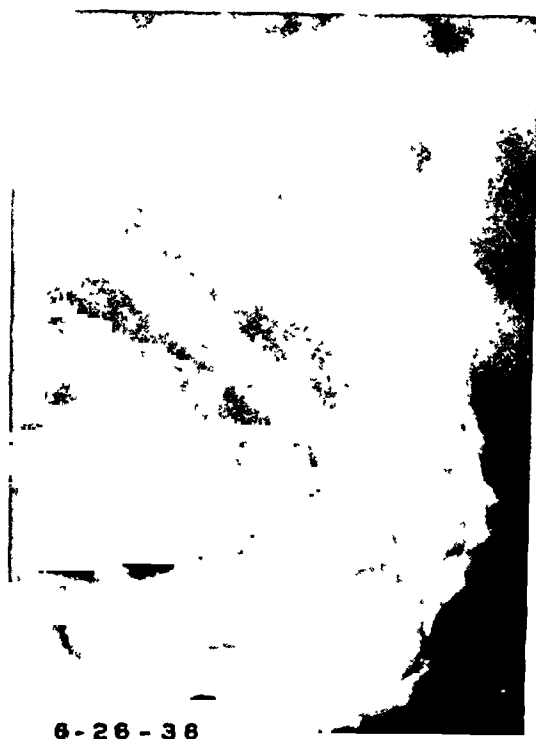


FIG. 4. CASL 4 STIFFENING OF THE LESSER CURVATURE, NARROWING OF THE STOMACH AND DISAPPEARANCE OF THE RUGAE JUST BELOW THE CARDIAC ORIFICE

(death due to an entirely unrelated condition) disclosed a hypertrophic gastritis only.

In Case 5, correctly diagnosed as diffuse gastric polyposis (Fig. 5), the underlying hypertrophic folds were obscured by the spectacular polypoid mucosal pattern.

Case 6 (Fig. 6) revealed an irregularity of the lesser curvature in September 1939, while x-rays taken in April 1940, 4 months after exploration with the removal of a gastric polyp, revealed in addition, unusually large rather soft folds of the body.

Certain features seem of value in the roentgenographic evaluation of giant

hypertrophic gastritis. In all six cases there was diffuse involvement of the stomach, the greater curvature being the principle site of the lesion. The mucosal folds were greatly thickened, indurated and enlarged, tending to produce an exaggerated saw-tooth appearance often with broad deep sharp notches, especially along the greater curvature. In Case 6 the lesser curvature was also affected. The rarity of lesser curvature involvement has been commented upon by Feldman (5). The marked softness of the enlarged rugae was a constant finding in every case except the third. Mucosal edema, due to

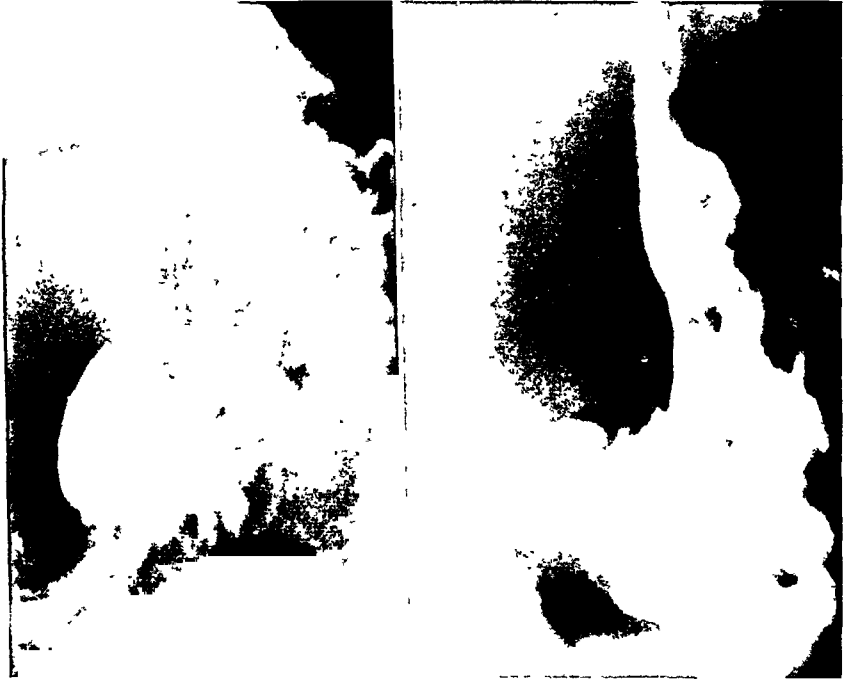


FIG. 5. CASE 5. DIFFUSE POLYPOSID, MORE MARKED IN MID-STOMACH

inflammation, hypoproteinemia, and perhaps trauma, may increase the size and consistency of the folds as in Cases 2 and 4. Pliability of the gastric walls with little impairment of peristalsis was noted in all of our cases with the exception of the third. Sprigg considered the flexibility, the maintained power of dilation and contraction, and the ability of the peristaltic waves to traverse the involved area without interference to be characteristic.

GASTROSCOPY

The gastric mucosa as seen gastroscopically in these cases is most interesting. Case 1 (Fig. 7) revealed a nodular appearance above the angulus, with thin

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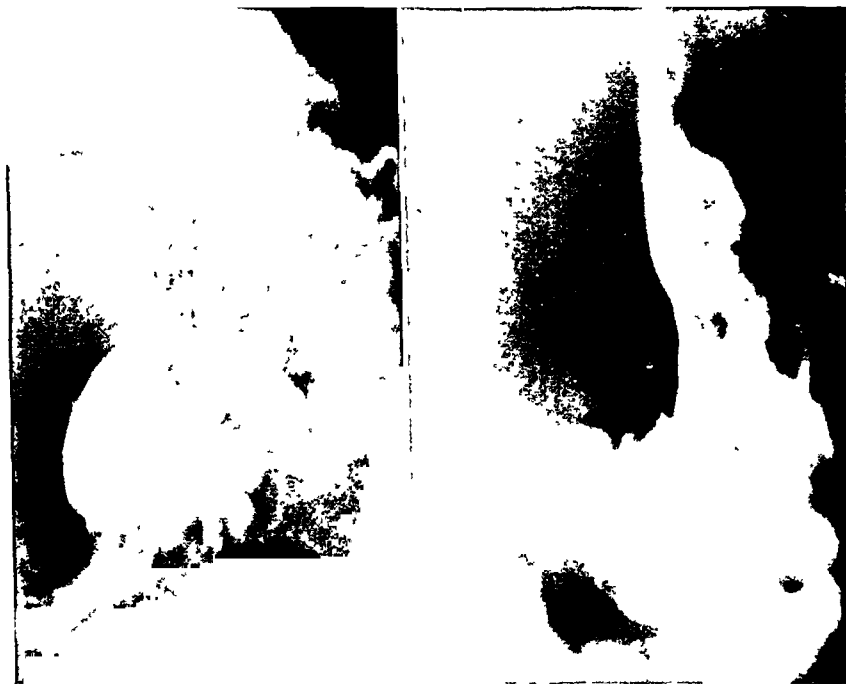


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GASTROSCOPY

The gastric mucosa as seen gastroscopically in these cases is most interesting. Case 1 (Fig. 7) revealed a nodular appearance above the angulus, with thin

greyish patches, in which blue blood vessels coursed. Histologic studies confirmed this. Along the upper part of the greater curvature and infringing on the anterior wall there was a bulge, nowhere sharply defined, covered with normal mucosa and extending from the mid-stomach to the cardia. An extra gastric mass, an unusual submucosal tumor or an unusual normal formation of the gastric wall were considered in the differential diagnosis. At the second examination 9 months later "In depth II the first change was noted on the greater curvature. A yellowish round ulcer was seen, close to the greater



FIG. 6. Case 6. (a) Large soft folds with a persistent collection of barium caught between the folds of the greater curvature.

curvature, the edge of which was red and the floor smooth. Above this a large tumor-like protrusion of the posterior wall was present. The mucosa covering this protrusion was slightly velvety in the lowest parts. Several shallow yellowish ulcerations were noted in the highest portion of the protrusion, while the tumor blended with the surrounding tissue without definite limit." The impression was a large ulcerating type IV carcinoma. Repeatedly the observer pointed out the blending of the tumor with the surrounding mucosa. The resected specimen contained no tumor (Fig. 11); histologically the mucosa was throughout uniform. Moersch and Weir (13) observed a similar tumor-like mass projecting into the lumen of the stomach, the sur-

face being covered with nodular slightly ulcerated mucosa, and attributed it to "redundant gastric mucosa simulating carcinoma".

In Case 2 the gastric folds were regularly enlarged, approaching the diameter of a little finger, and seemed to extend from the angulus to the cardia. The mucosa was edematous, hyperemic, and in its entirety resembled the surface of the cerebrum. Numerous fold crests were the seat of a diffuse ulcerative process with small whitish erosions covered with grey purulent exudate. The gastroscopic impression of giant hypertrophic gastritis was substantiated by the gross findings. In Case 3 (Fig. 8) also there was marked enlargement and prominence of all the gastric folds with unusual regularity in their size, shape and appearance. They appeared uniformly thickened, as if infiltrated by some



FIG. 7



FIG. 8

FIG. 7. Case 1. Tumor-like protrusion of the posterior wall with shallow ulcerations (7 o'clock). Nodular appearance of the mucosa distal to the protrusion.

FIG. 8. Case 3. Marked regular enlargement of the gastric folds, approaching the diameter of a little finger. Edema of the mucosa with abundant greyish exudate over the crests and between the folds. Note the resemblance to the surface of the cerebrum.

neoplastic process. The mucosa was hyperemic, dull red and finely nodular. These descriptions are typical of the gastroscopic appearance of giant hypertrophic gastritis. Heeks and Gibbs (14) referred to the folds as "finger like" and likened their appearance to cerebral convolutions.

In Case 4 (Fig. 9) outspoken changes in the greater curvature, anterior wall and lesser curvature were attributed to a huge tumor of peculiar structure. These changes consisted of many spongy nodules and folds separated from one another by small dark creases. Numerous pits and dark depressions resembling small ulcerations were observed. The mucosal folds appeared dark red and nodular. Carcinoma and lymphoblastoma were considered likely although the soft spongy appearance elicited considerable comment. The gross specimen resembled that of Cases 2 and 3. The marked proliferation of the epithelium had produced the tumor-like folds and the soft spongy cellular appearance so suggestive of neoplasm. The increased cellularity present in

this case and marked in Case 3 may account for the granularity and spongy appearance seen at gastroscopy.

In Case 5 there were numerous round or oval polyps of varying size, some without a visible base while others, apparently with short pedicles, peppered the gastric mucosa from the angulus to the cardia; none were observed in the antrum. The surfaces were smooth and covered with adherent patches of mucus. No gross evidence of malignant change was detected. The gastric mucosa everywhere was thinned and its color was grayish pink. The impression was that of adenomatous polyposis. Histologic study, however, revealed hyperplastic polyp formations in giant hypertrophic gastritis.

In Case 6 (Fig. 10) gastroscopy revealed stiff, nodular, beady folds of



FIG. 9



FIG. 10

FIG. 9. Case 4. Spongy nodules and folds. The folds are nodular, stiff, and appear infiltrated. Histologic study revealed marked cellularity and cystic formations of the mucosa.

FIG. 10. Case 6. Stiffened fold with many nodes on its surface. At operation hyperplastic polyps were found on the crests of the hypertrophied folds.

the greater curvature and the posterior wall while a huge fold-like protrusion, stiffened and infiltrated, with many nodes on its surface was noted in the cardiac portion. The polyps noted at operation were not discernible at gastroscopy, being described as nodes. Schindler (15), has observed that true adenomas usually appear as pedunculated or broad based, red, mucosal covered, elevations in an atrophic background. Hyperplastic polyps, on the other hand, are not well defined and blend with the surrounding often swollen mucosa.

While it is evident that the gastroscopic differentiation of tumoral gastritis, lymphoma and carcinoma is extremely difficult and, at times, impossible, the six cases described were strikingly similar. It is quite possible that with increased awareness of the condition, more accurate diagnoses will be made.

PATHOLOGY

The variations in the pathologic features were considerable and most instructive.



FIG. 11. CASE 1. ENORMOUS CONCENTRIC FOLDS OF MUCUS MEMBRANE IN THE MID-STOMACH. MARKED MAMMILLATION OF THE MUCOSA

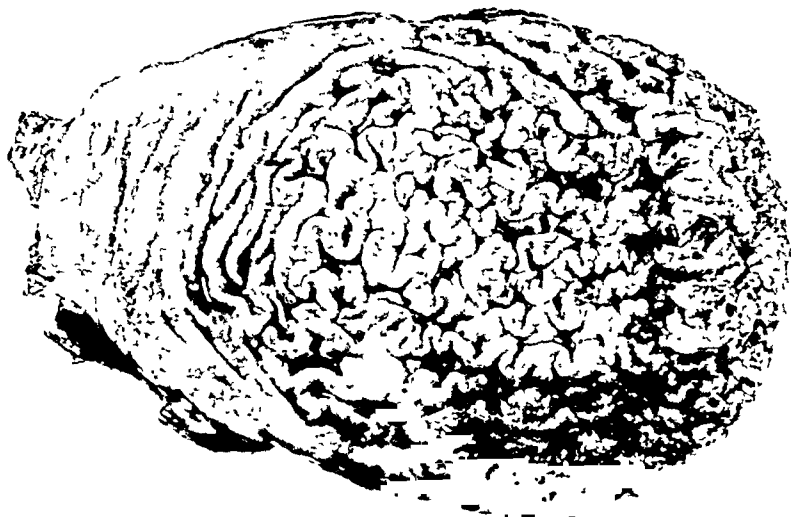


FIG. 12. CASE 2. STOMACH OPENED ALONG THE GREATER CURVATURE SHOWING THE HUGE PEBBLY RUGAE, ENLARGED AND TIGHTLY PACKED TOGETHER

Gross Appearance. In Case 1 the concentric folds of mucous membrane were arranged in a most unusual formation (Fig. 11). They varied in height from 1.5 to 3 cm. and covered an area of 8 x 7 cm. The mucosal appearance was pavement-like due to small mammillary structures; the serosal surface was not unusual. In Case 2 the stomach was grossly enlarged with thickened walls through which the wavy rugal pattern was discernible. The serosal surface was smooth but excessively vascular. When opened along the lesser curvature huge violaceous pebbly rugae, grossly enlarged and packed tightly

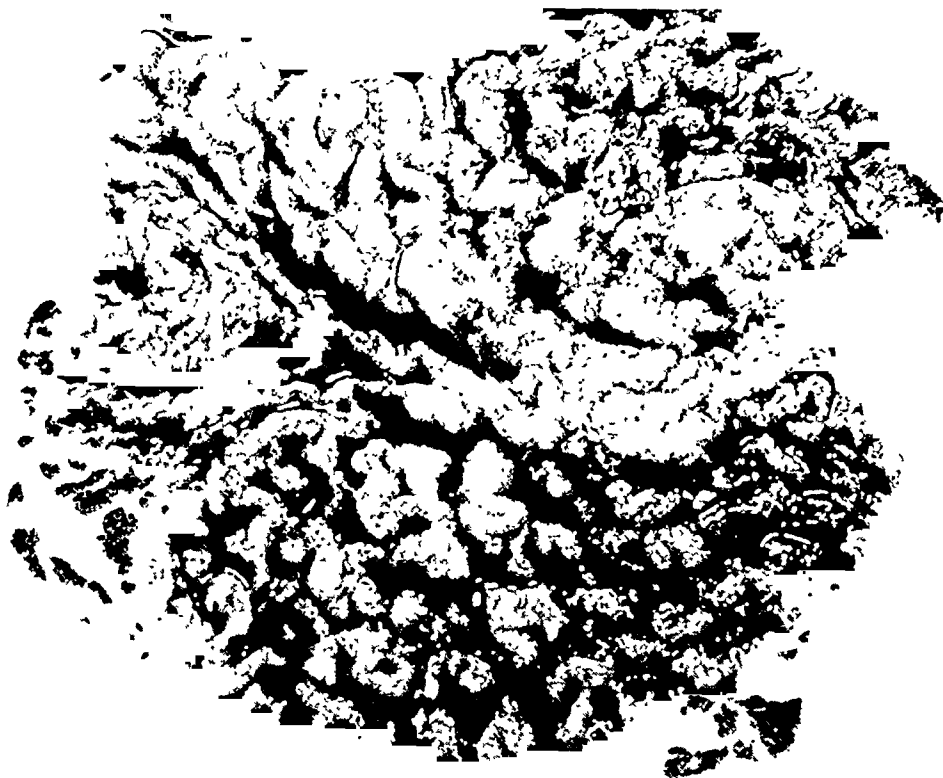


FIG. 13. CASE 3. STOMACH OPENED ALONG THE GREATER CURVATURE SHOWING THE "CEREBRAL CONVOLUTIONS"

together, were revealed (Fig. 12). The antral area was least involved; its mucosa, while cobblestoned in appearance, was smoother than elsewhere. The mucosa was everywhere freely movable on the underlying structure without induration; thick tenaceous mucus abundantly covered its surface. At operation in Case 3 the serosal vessels were unusually prominent and the stomach was quite enlarged. The wall was markedly thickened throughout due to the soft movable tissue in its luminal surface except along the lesser curvature where it was quite firm. This is in agreement with the observations of Cole (8) who noted that the serosal surfaces of such stomachs sometimes displayed characteristic networks of blood vessels forming brilliant red lines

against a pinkish white serosa with associated enlargement of the entire stomach. The region involved was softer to the touch than a neoplasm; indeed it felt like a bunch of "fish worms". On opening the enlarged stomach along the greater curvature, rugae appeared not unlike convolutions of the brain (Fig. 13). The mucosa was finely granular, reddish purple and freely movable over the muscularis. The rugae were largest and most closely pressed together along the lesser curvature, some measuring 2.5 to 1.5 cm. in height and width. In Case 4 marked enlargement of the stomach was again noted, while the widespread diffuse prominence of the folds resembling cerebral

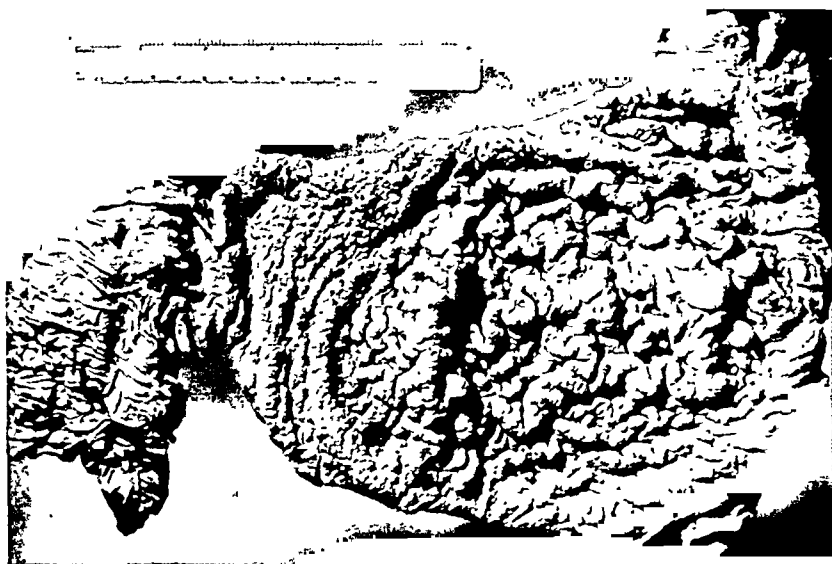


FIG. 14. CASE 4. MARKED ENLARGEMENT OF THE MUCOSAL FOLDS RESEMBLING THE CONVOLUTIONS OF THE CEREBRUM EXTENDING FROM A FEW CENTIMETERS BELOW THE CARDIA ALMOST TO THE PYLORUS

convolutions was striking (Fig. 14). In these 4 cases the increase in the size of the stomach, the similarity of the folds to the cerebral convolutions in Cases 2, 3, and 4, the mobility of the mucosa, the abundant formation of mucus and the diffuse involvement are noteworthy.

The classic description of this unusual condition first given by Menetrier has not been improved. According to Heek and Gibbs (14) who quote Menetrier "This is a form of diffuse mucosal hypertrophy in which the glands assume considerable proportion with diffuse and general alterations involving large areas of tissue which rise above the rest of the stomach and produce a tufted and wavy appearance with large folds. In the opened stomach the mucosal folds present a marked resemblance to the cerebral convolutions."

The gross specimen of Case 5 consisted of the mid-portion of the stomach, the opened specimen measuring 10 x 19 cm. The mucosal surface (Fig. 15) revealed twenty-two pedunculated or sessile polyps spherical to elliptical in shape, varying in size from 8 x 5 x 3 mm. to 22 x 18 x 15 mm. The surface, from which the largest polyps originated was covered with hypertrophic pale pink rugae. The remaining mucosa was less hypertrophied but had many coarse thickenings of its rugae and several smaller sessile polyps. Thick tenacious mucus bathed the epithelial surface and the mucosa was not fixed

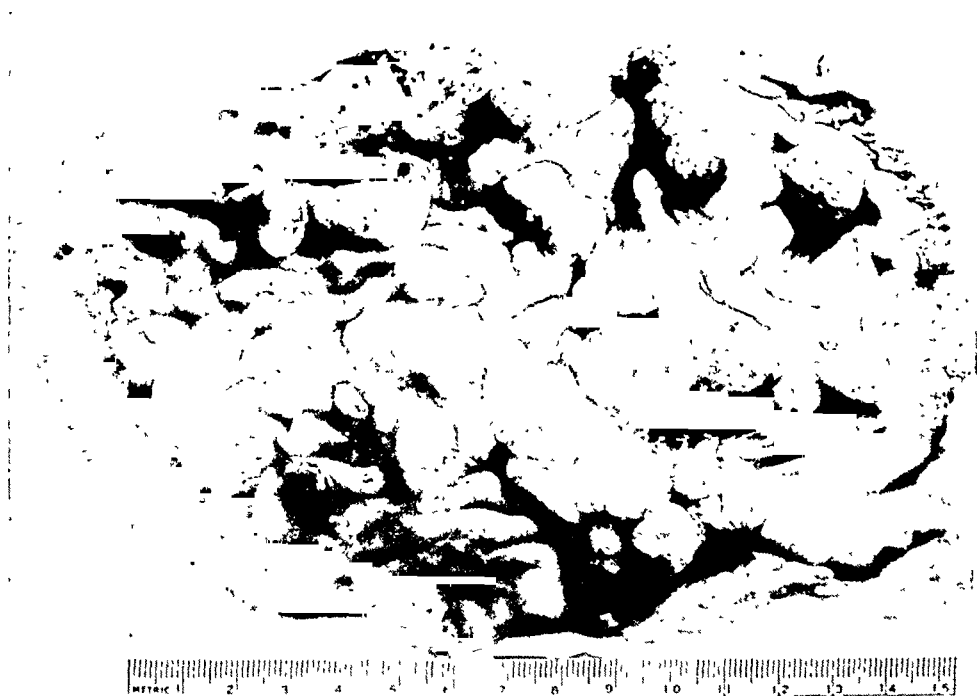


FIG. 15. CASE 5. MID-PORTION OF STOMACH WITH PEDUNCULATED AND SESSILE HYPERPLASTIC POLYPS AND HYPERTROPHIED FOLDS

to the underlying tissues. In Case 6 according to the surgeons' description, the gross findings were similar to those in Case 5 with fundic mucosal hypertrophy, numerous great folds resembling papillomatous structures, and papillomas with narrow stalks and cauliflower-like tops, measuring up to 1.5 cm. in diameter. The stalks were longer and thinner than in Case 5.

*Histologic Observations.*² The stomach in Case 1, which displayed huge folds of mucosa with marked mammillation (Fig. 16a) showed relatively normal proportions of glandular elements with little evidence of metaplastic transformation (Fig. 16b). The interstitial cellular exudate, abundant only between the mucous crypts, contained large numbers of eosinophiles. The nuclei of some of the mucous cells were displaced from their basal positions

² The sections for Figures 17, 18, 19, 24 and 25 were prepared by Henry Sallmen, Department of Surgery.

and were palisaded, an appearance suggesting crowding of the epithelial cells in the crypts. It should be noted, however, that atrophic mucosal changes were present in the antrum. The thickened, highly vascularized and edematous submucosa was also noteworthy. The stomach in Case 2 revealed in-



FIG. 16. Case 1. (a) (Upper.) (Mag. 13X). Marked hyperplasia of the glandular epithelium showing the mammillated changes. (b) (Lower.) (Mag. 135X). Hypertrophied mucosal tufts with marked cellular infiltration, particularly of eosinophiles.

creased thickness of the muscular coats and submucosa with fibrotic changes in both (Fig. 17 and 18). The glandular portions of the folds were somewhat hypertrophic and the folds were redundant but the relative proportions of cell types were nearly normal. A few nests of glands penetrating the muscularis mucosae were noted, presumably in areas where this structure was decreased in physical resistance. These glands, however, did not appear abnormal.

In Case 3 there was pronounced reduplication of folds and mucosal redundancy. On cross section, the resemblance of the folds to papillomata was striking (Fig. 19). Focally, significant alterations of cellular type and glandular structure were found, with columnar and goblet cells of the intestinal



FIG. 17. CASE 2. (MAG. $2\frac{1}{2}\times$.) MARKED REDUNDANCY OF THE MUCOSAL LAYER
Higher magnification reveals in most places an appearance similar to the mucosa of Fig. 16 (a and b)



FIG. 18. CASE 2. (MAG. $2\frac{1}{2}\times$.) INCREASED THICKNESS OF THE MUSCULAR COATS WITH FIBROPLASIA AND EDEMA OF THE SUBMUCOSA

type replacing the acid-secreting and pepsinogenic varieties. In many areas the mucous cells had displaced nuclei, suggesting hyperplasia (Fig. 20). Nevertheless, in considerable areas the glandular cell pattern was relatively normal. Another feature was the presence of numerous cystic glands, many of them near and some of them protruding through the muscularis mucosae.



FIG 19 CASE 3. (MAG 4X) MARKED PAPILLAMOTOUS PROLIFERATION OF THE GASTRIC MUCOSA

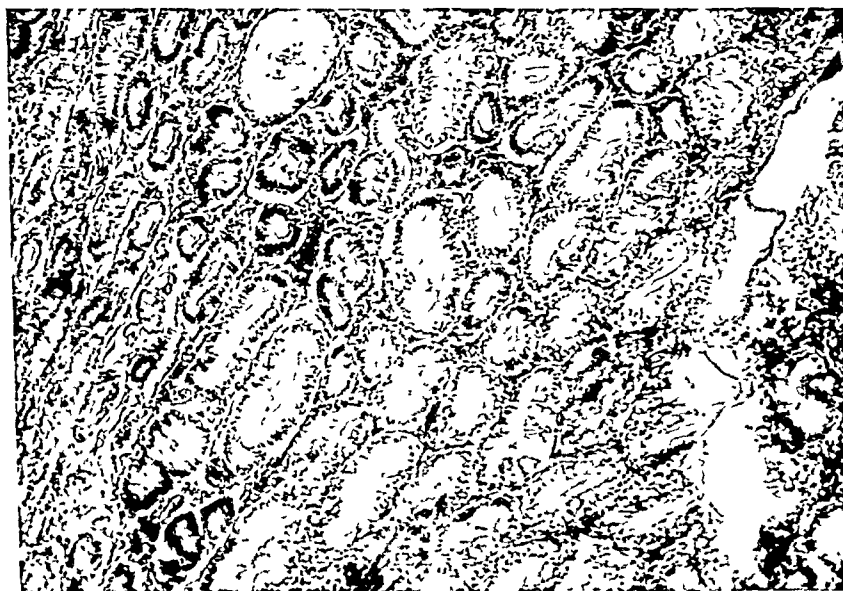


FIG 20 CASE 3 (MAG 145X) HYPERTROPHIED GLANDS OF COMPLEX STRUCTURE SHOWING INCREASED CHROMATISM OF THE NUCLEI, DISORDERLY, CROWDED NUCLEI, AND CONVERSION OF SOME GLANDS INTO CRYPTS, RESEMBLING THE COLONIC TYPE

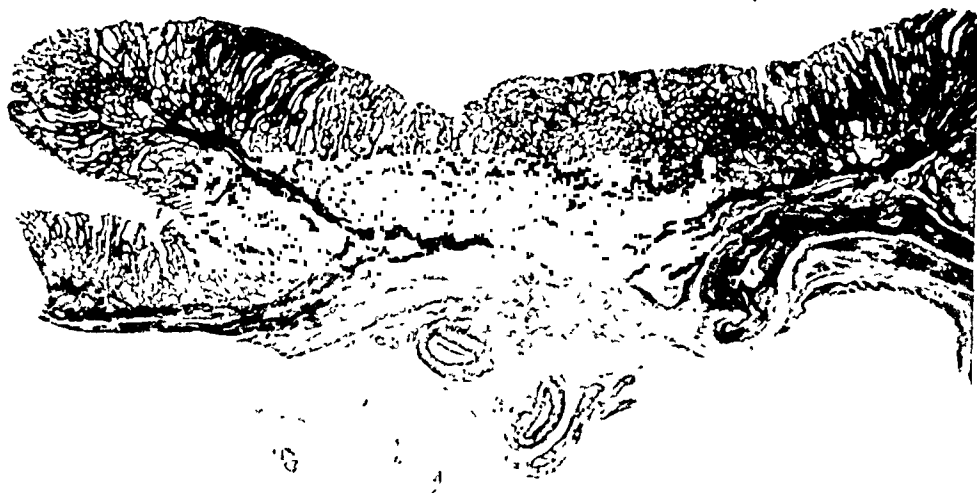


FIG. 21. CASE 4. (MAG. 10X.) TUMOR-LIKE PROLIFERATION OF THE EPITHELIUM TO THREE TIMES ITS NORMAL SIZE



FIG. 22. CASE 4. (MAG. 60X.) ELONGATION AND HYPERTROPHY OF THE MUCOUS PORTION OF THE GLANDS

Cystic formations with marked deformation of the adjacent non-cystic glands, extending to the muscularis. Marked replacement of acid secreting and pepsinogenic cells by intestinal type of goblet cells.



FIG. 23. Case 4. (Mag. 600X.) Note the Russell's bodies (large cells with eccentrically placed nuclei and filled with amorphous hyaline material) which form part of the inflammatory infiltrate.



FIG. 24. CASE 5. (MAG. $\times 7$.) HYPERTROPHIED THICKENED MUCOSAL FOLDS AND SESSILE POLYPOID STRUCTURE
Note the increase of fibrous tissue in the wall of the stomach

The exudate was similar in character and distribution to that in Case 2, but was more extensive in the submucosa, at least focally (Fig. 19). Edema and venous congestion were pronounced in the mucosa and submucosa. An interesting feature was the presence of small erosions, some of them healing, of the type thought by Konjetzny (16) to be the precursor of peptic ulcers.



FIG. 25. CASE 5. (MAG. $\times 7.5$.) HYPERPLASTIC POLYP WITH A LONG STALK, PROJECTING FROM A HYPERTROPHIED MUCOSAL FOLD
Compare gross structure, Figure 15

These were located in the niches between folds, or between coarse mammillations, rather than on exposed surfaces.

In Case 4, the gastric mucosal folds were less redundant than in Cases 2 and 3, and glandular hypertrophy was largely responsible for the thickness of the folds (Fig. 21). The metaplastic transformation of the mucosa, with cyst formation was striking, as illustrated in Figure 22. Here and there a few parietal and pepsinogenic cells remained, but the glands for the most part appeared like huge mucous crypts lined by mucus-filled cells. Some of

the cysts contained leukocytic exudate but interstitially the cells were mostly plasma cells, many of them huge cells packed with Russell's bodies (Fig. 23). The submucosa was fibrotic, and exudate was scanty save in the mucosa.

Case 5 (Figs. 24-26). There was very marked metaplastic transformation of the glands to the colonic type on the less conspicuous folds as well as on



FIG. 26. CASE 5. (MAG. $6\frac{1}{2}\times$.) HYPERPLASTIC POLYPS WITH CYSTIC FORMATIONS AND EPITHELIAL HYPERTROPHY

the large ones, with their polypoid appendages. In some regions, this metaplasia was associated with mucosal thinning, fibroplasia, and distortion of the glandular pattern, features so often seen in atrophic gastritis, nevertheless hypertrophied glands of more normal cellular composition persisted in the sessile and projecting polypoid structures, as well as on many of the folds. However, acid-forming cells were nowhere very numerous. Mucosal fibroplasia appeared to be responsible for much of the deformation of the glandular pattern (Figs. 25 and 26). Especially in the large polyps this deformation

had led to the production of adenoma-like nodules. The mucosal exudate was chiefly of mononuclear cells, but there were some areas with eosinophiles and neutrophiles, especially in the regions with large and cystic glands. Exudates were inconspicuous in the submucous and muscular coats, of which the former was especially fibrotic. In some regions fibrous tissue was increased in the outer tunics (Fig. 24). The submucosa contained many dilated lymphatic channels and many sclerotic veins. The arteries were more nearly normal.

It should be emphasized that none of the many polyps examined had the relative uniformity, glandular and cellular, of benign gastric adenomas and papillomas. In none was there any evidence of malignant transformation. Histologically the papillomas in Case 6 proved to be hyperplastic rather than adenomatous and were associated with a severe hypertrophic gastritis. Alteration of the mucosal pattern was not pronounced but interstitial and intra-glandular exudate was abundant.

DISCUSSION

The significant pathologic findings in the first four cases were the reduplication and redundancy of the mucosa with a glandular structure approaching normal as in Cases 1 and 2 and the increase in glandular hypertrophy to form the folds as in Cases 3 and 4. In the latter two, the marked alteration of glandular structure with replacement of the pepsin and acid forming cells by intestinal goblet cells was widespread and marked. Thickening, increased vascularization and edema of the submucosa was found in Case 2 while the presence of nests of normal cells below the muscularis mucosae was noted in Cases 2, 3, and 4. The microscopic description of Menetrier's original cases, as cited by Heeks and Gibbs (14), reveals great similarity. The penetration of the muscularis mucosae as noted in Cases 2, 3, and 4 was not found by Menetrier. It does not suggest neoplasm; it is equivalent to the type of herniation commonly seen in the secondarily contracted gall bladder producing the gland spaces which are called the crypts of Rokitansky.

In a discussion of the etiology, Feldman (5) suggests that the fibrosis of the submucosa and muscularis result in contracture which contributes to the polypoid appearance of the gastric folds while Hinkel (17) found the rugal height to be related to the condition of the muscularis mucosae with variations in mucosal thickening determining the polypoid character of the surface. Sprigg (6) describes changes suggesting a reparative hyperplasia in atrophic hyperplastic gastritis with associated increase of connective tissue and glandular elements. Hyperemia and edema were frequently noted. Stewart, cited by Pearl and Brunn (18), suggests the inheritance of a recessive characteristic, in mice of a certain strain which frequently is associated with the development

of adenomatous, hypertrophic and hyperplastic overgrowth of the rugae, but this inherited tendency could not be demonstrated in humans by Pearl and Brunn.

The disordered growth, marked alteration of cellular types with intestinal cells replacing the normal varieties are striking; suggesting pre-neoplastic changes. In none of the cases in this series, however, was there any evidence of malignant changes. Warren and Meissner (19) have called attention to the changes in the cellular components, in gastritis, suggesting that marked changes may be comparable to pre-malignant conditions in other parts of the body. Stout (20) in a discussion of pre-cancerous gastric lesions noted increased numbers of mucus cells in the changing mucosa, which may be polypoid in formation resembling patchy hyperplasia of mammary duct cells in sub-clinical forms of cystic disease of the breast, in carcinoma containing stomachs. In spite of the attractive theoretical considerations the relationship of gastritis and carcinoma is entirely unknown. Two of Spriggs (6) 12 patients later developed carcinoma of the colon while the gastric lesions remained unchanged.

In 4 cases of "polyadenoma en nappe" collected (18) in a review of the literature from 1926 to 1942, one was associated with diffuse adenocarcinoma, while in three cases of adenomatous polyposis there was associated hypertrophic gastritis.

Diffuse giant hypertrophic gastritis with areas of hypertrophy forming multiple polypoid lesions are not common; the gross differentiation of these from polypoid adenomas is difficult or impossible. In a review of 37 adenomatous polyps Pearl and Brunn (18) found evidence of malignancy in 19. Stewart found 28 per cent neoplastic in 47 cases, 20 per cent of which were multiple. Eliason and Wright noted malignancy in 20 per cent of 20 cases. Sprigg (6) however, reports six non-operated gastric polyps demonstrable on x-ray and followed for 2 to 12 years, without progression. In cases 5 and 6 of the present series, there was no evidence of neoplasm. Borrmann believed that gastritis is rarely the site of adenomatous polyps, that polypoid hyperplastic nodules may result however, and that the occurrence of malignant changes in these hyperplastic polyps is uncertain.

The evidence regarding the congenital and inflammatory origin of polyposis is controversial (21), but general experience would indicate that adenoma formation in hypertrophic gastritis is unusual. In the formation of hyperplastic polyps Sprigg (6) suggests that "in proliferating crypts of gastritis small prominences are formed and these are pressed together lifting the mucous membrane, dragging the muscularis mucosae with it and a peak is formed." Conceivably peristaltic propulsion in the stomach creates a mechanical drag on the small sessile lesion which eventually results in a pedunculated mass. The findings in Case 5 favor this hypothesis. Sprigg commented on the drawn

out inflamed mass of elongated and broadened crypts and glands with a normal membrana propria and muscularis which he found in these lesions. Pearl and Brunn (18) point out that inflammatory polyps are often not well differentiated into head and stalk. On section the submucosa is found to take no part in the growth as a connective tissue core and the lesion is usually firm, resting solidly on the submucosa. They state that in neoplastic polyps the muscularis may enter the stalk of the adenoma forming one of the distinguishing features from hyperplastic polyps and that the abnormal tissue is usually more sharply demarcated from the surrounding tissue than in inflammatory polyps. Case 6 displayed definite head and stalk formations with a central core and in Case 5 the central core of muscularis mucosae and submucosa is prominent in the stalk. Primary degeneration of the glandular epithelium without inflammatory change has been reported by Sharpless (22), Berg (23), and others from dietary deficiencies. Overactivity of the epithelium may appear in the reparative phase with focal mucosal hypertrophy and hyperplasia.

Marked edema of the gastric mucosa has been noted in dietary deficiency; the role of hypoproteinemia must be considered. In Case 4 there was a constant peripheral edema and a total plasma protein level of 4.9 gm. per cent with an A/G ratio of 1.74. In Case 2 spectacular decrease in the plasma protein level was noted with a drop from 5.09 grams to 3.61 grams per cent in 16 days. Following supportive measures the level returned to 6.36 and after operation remained at a level of 6.16 gm. to 6.45 gm. per cent. While dietary deficiencies could account for the changes in Case 4 the rapid lowering Case 2 is harder to explain. One might postulate unusual plasma loss from the abnormal gastric surface. Del Solar, Brodsky and Donoso (24), describe a "pseudoneoplastic" gastric lesion in a patient with severe malnutrition diagnosed as carcinoma on x-ray examination. The patient was treated for the nutritional disturbance and the gastric tumor disappeared. The patient later died with pulmonary tuberculosis; at autopsy the only gastric lesion was hypertrophic gastritis.

From the standpoint of the clinical diagnosis, differentiation from carcinoma was not satisfactory by gastroscopy or by x-ray in the cases presented. In Cases 1, 3 and 4, the unusual gastroscopic appearance was noted; in Case 2 a definite diagnosis of tumoral gastritis was made; in Case 3 the likelihood of this entity was strongly considered. In Case 1 the diagnosis of carcinoma was made at the second gastroscopy. The x-ray examinations in Cases 1, 2, 4 stressed the softness of the infiltrated folds. In Case 1, followed over two years, the x-ray findings were interpreted as indicating a loss of the rugae and replacement by a polypoid mass. The resemblance to carcinoma was marked. On the other hand, in four patients followed by Sprigg for a five year period, disappearance or marked improvement of the gastritis occurred following dietary measures and roentgen therapy. In one the recessive changes

took place in an observation period of about 16 months. One of us has noted in a patient with duodenal ulcer severe tumoral gastritis, at gastroscopy, confined to the lower portion of the stomach. This finding was confirmed by x-ray. The surfaces of the hypertrophic folds displayed many up to 3 mm. nodular elevations. The patient then received roentgen therapy to the stomach to lessen acid secretion, as part of the therapy employed for the duodenal ulcer. Several months later a second gastroscopy disclosed the folds to be much smaller and the nodularity previously noted had disappeared. Schindler has reported a case of severe hypertrophic gastritis which improved after x-ray therapy. These findings suggest the possible value of x-ray in the therapy of giant hypertrophic gastritis. Further study of the problem is indicated.

SUMMARY

Six cases of giant hypertrophic gastritis are described, two with superimposed hyperplastic polyp formation. The difficulty in differentiating this condition from neoplasm is evident from the fact that all six were subjected to operation. The symptomatology is indefinite. Anatomically, roentgenologically and gastroscopically, the resemblance of the gastric folds to the convolutions of the brain is striking and is, perhaps, the most salient feature.

Histologically, redundancy of the mucosa and marked hypertrophy of the glandular structures are outstanding features with cyst formations and metaplasia to the intestinal type of epithelium. The pepsinogen and acid forming cells are replaced by the more primitive type. Fibroplasia with increase of connective tissue and edema were prominent features. In two cases redundancy was outstanding while in two others hyperplasia and increased thickness of the mucosa were remarkable. Multiple polyps developed in two cases.

CASE REPORTS

Case 1, (7). W. T., a white male aged 71, was admitted in December, 1936, with a history of a massive upper gastrointestinal hemorrhage two years prior to admission followed by persistent intermittent epigastric fulness and bloating, lasting several days and followed by a period of freedom from symptoms. The pain occurred several hours after meals and was relieved by alkalis and milk. The routine physical and laboratory examinations were within normal limits. The stools consistently showed a trace of occult blood while gastric analysis (histamine) revealed a maximum free acidity of 40 clinical units.

X-ray (F. E. T.) December 10, described the gastric rugae as extremely prominent, especially along the greater curvature. The folds were pliable but could not be obliterated by pressure.

At gastroscopy December 19, 1936 (R. S.) it was noted that "above the angulus a kind of nodular appearance suggested remnants of normal mucosa in thin greyish patches, in which blue blood vessels coursed. Numerous mucosal hemorrhagic areas

were seen exuding free blood into the stomach. Along the upper part of the greater curvature and infringing on the anterior wall a bulge, which was nowhere sharply defined, covered by smooth normal mucosa was noted. This extended from the middle of the greater curvature to the cardia."

The patient was placed on a modified Sippy regimen with relief of symptoms. However, at x-ray (F. E. T.) February 19, 1937 "the pliable irregularity of the greater curvature was again noted."

In September, 1938, the patient re-entered the hospital with a marked recurrence of the same symptoms and a weight loss of 23 pounds. The physical examination and laboratory findings were again essentially normal. The plasma proteins were 6.34 gm. per cent; the A/G ratio 1.52. Roentgenologically (P. C. H.) the greater curvature of the stomach was described as grossly irregular but not stiff, the grossly abnormal rugae as not incompatible with an unusually soft neoplasm. Gastroscopecally (R. S.) a yellowish round ulcer was seen close to the greater curvature the edge of which was red and the floor smooth. A tiny erosion was seen in the mucosa distal to the ulcer. The mucosa surrounding the ulcer seemed stiff. Above this region a large tumor-like protrusion of the posterior wall was seen. The mucosa covering this protrusion was slightly velvety in the lower parts. Several yellowish shallow ulcerations were seen in the highest portion of the protrusion. Fresh hemorrhage was observed at this site. The tumor blended with the surrounding tissue without definite limit.

Impression: "Large ulcerating carcinoma Type IV of the posterior wall of the body. Diffuse atrophic gastritis."

A repetition of the x-ray examination by (F. E. T.) reported that "peristaltic wave progressed the entire length of the lesser curvature and through that portion of the greater curvature below a rounded filling defect which protruded into the posterior wall of the stomach above the level of the angle. The rugae of the upper portion of the stomach are completely destroyed and replaced by a large polypoid mass. The presence of an infiltrating carcinoma is likely and the question of the relationship of atrophic gastritis as a precursor to carcinoma is considered.

The patient continued to complain of burning epigastric pain consistently relieved by the ingestion of alkalis. At operation the stomach was found to be redundant; palpation revealed large coarse palpomatous folds of the mucosa, no definite hard masses and no metastases to the liver could be detected. Partial resection was carried out. The patient died of peritonitis. The pathologic findings have already been described.

Case 2. White, male, aged 59, was admitted to the service of Dr. H. P. Jenkins at the Billings Hospital November 19, 1945, with a history of bouts of mid-epigastric pain for 35 years. Partaking of food produced, while abstention prevented this distress. From 1930 to 1945 the attacks were mild and infrequent but in November, 1945, the patient noted severe mid-epigastric pain one half hours after meals, 15 to 20 minutes in duration, associated with severe vomiting. Physical examination was non-contributory except for epigastric tenderness. The urine was normal; the blood counts were within normal limits; the blood sugar was 79 mg. per cent; the plasma

protein 7.45 gm. per cent; and the gastric free acidity 106 clinical units (histamine). Stool examination revealed 3 plus occult blood by the benzidine test.

X-ray examination (P. C. H.) November 9, 1945, repeated November 19, demonstrated a small penetrating ulcer of the lesser curvature with an extensive irregular filling defect along the greater curvature thought to be due to a soft polypoid carcinoma rather than edema.

Gastroscopecally (S. N. M., November 21 and December 4, 1945) the gastric folds presented an unusual appearance, being regularly enlarged and approaching the diameter of a little finger. The mucosa was edematous, and hyperemic; the picture in its entirety resembled the surface of the cerebrum. Numerous fold crests contained small whitish erosions covered with grey purulent exudate. The marked

TABLE 1

DATE	TOTAL PROTEIN	ALBUMIN	GLOBULIN	A/G RATIO
	gm. %	gm. %	gm. %	gm. %
11-19-45	5.09			
12- 5-45	3.82			
12- 6-45	3.61			
12- 7-45	3.89	2.89	1.00	2.89
12-10-45	3.78	2.33	1.45	1.61
12-13-45	4.47	3.00	1.47	2.04
12-15-45	4.49	3.01	1.98	1.52
12-18-45	5.28	3.70	1.58	2.34
12-19-45 (a.m.)	5.30	3.28	2.02	1.62
12-19-45 (p.m.)	5.40	3.41	1.99	1.71
12-26-45	6.36			
Operation December 27, 1945—total gastrectomy				
1- 4-46	5.42	3.65	2.77	1.32
1-16-46	6.16	4.40	1.76	2.50
1-25-46	6.12			
2- 9-46	6.45			

prominence of the folds extended to the cardia. This was interpreted as a diffuse giant hypertrophic gastritis.

At the third x-ray examination (P. C. H., November 29, 1945), the findings were similar although the previously observed lesser curvature lesion was smaller and, in addition, a deformity of the duodenum was found. At the fourth x-ray examination (P. C. H., December 1, 1945) the softness and widespread distribution of the gastric folds were thought to argue against the former idea of neoplasm and for hypertrophic gastritis. The apical deformity of the duodenal bulb persisted.

On December 3rd the patient spontaneously developed thrombosis of the left saphenous vein which responded favorably to venous ligation December 7th. Plasma protein determinations at this time revealed an unusually low level but clinically there was little evidence of such a decrease.

Table 1 shows the change in plasma protein from November 19, 1945, to February 9, 1946.

It was postulated that the plasma loss conceivably occurred through the unusual gastric mucosa much in the same manner that serum is lost from the denuded surface of an extensive burn. In view of this thought and the continuation of the patient's symptoms exploratory laparotomy was performed by Dr. H. P. Jenkins on December 27, 1945. At operation "the stomach was enlarged, and unusually soft and velvety throughout. An area of thickening was palpated in the anterior wall of the pylorus while the entire pylorus was diffusely indurated". An unexpected complication consisted of a herniation of a large part of the jejunum through a window in the mesentery of the midportion of the small bowel. The hernia was reduced and a total gastrectomy was carried out because of the extensive gastric involvement. Recovery was uneventful; the patient was ambulatory three days after operation; the plasma proteins returned to a normal level and the patient has had no significant complaints since operation.

The gross specimen consisted of the entire stomach measuring 14 cm. along the lesser curvature and 45 cm. along the greater curvature, appearing grossly larger than usual. The gross findings have been previously described.

The histologic sections showed moderate to marked thickening of the muscularis. The mucosa was thrown-up into tightly packed finger-like rugae, measuring from 0.5 to 1.5 cm. in height. The cores of most rugae were composed of extensions from the muscularis mucosae and prolongations of the submucosa which had undergone considerable fibroplasia. Throughout the cellular detail was similar, being characterized by tightly packed, hypertrophied glands. The glands were greatly elongated, but were lined mainly by normal appearing cells. The cells lining the fovea contained large amounts of mucus and mucus formed glacial masses between the rugae, dilating the mouths of the glands into tortuous patterns. Many of the mucous cells were of goblet or colonic type. In places, columnar or cuboidal mucous cells were seen, deep in the mucosa and even forming dilated cystic spaces in the submucosa. These spaces contained mucous and cellular debris. These changes were most noticeable in the antral areas where marked focal hypertrophy of the Brunner glands was also present.

Throughout the gastric wall and even in the muscularis propria were many lymphocytes, eosinophils, some plasma cells, and occasional Russell's bodies. Lymphocytic follicles were abundant.

Case 3. White, male, aged 41, was admitted to the service of Dr. W. E. Adams because of gnawing epigastric discomfort relieved by food, a sensation of fullness relieved by eructation, and a recent weight loss of about ten pounds. The gastric free acidity was 20 units. X-ray examination of the stomach was reported as showing a completely irregular polypoid protrusion of the body of the stomach with stiffening of the posterior wall. No definite crater was seen but there were many more or less constant collections of barium between the elevations of the mucosa. The roentgenologic interpretation was multiple polyps and almost certainly polypoid carcinoma. Gastroscopecally the pyloric channel was clearly visualized. There was marked enlargement and prominence of all the gastric folds with unusual regularity

in their size, shape and appearance. The folds appeared to be uniformly thickened as if infiltrated by some neoplastic process extending to the cardia. No surface ulceration was detected; the entire mucosa was hyperemic dull red and finely nodular. The marked regularity in the size and shape and appearance of the thickened and enlarged folds was noteworthy.

At operation Dr. W. E. Adams found the stomach quite enlarged, the serosal vessels prominent and the wall markedly thickened throughout due to soft movable tissue in its luminal surface, except along the lesser curvature where it was quite firm. Enlarged lymph nodes showed only lymphoid hyperplasia in frozen section. Total gastrectomy was followed by an uneventful recovery. The gross appearance has been already detailed.

Along the lesser curvature of the gastric wall where the mucosa was grossly noted to be firm and fixed to the underlying structures, two ulcers were detected. One was a comparatively small superficial healing erosion which had become lined by simple columnar epithelium. In its floor considerable inflammatory reaction was present. The larger ulcer occupied the valley between two very tall rugae, and was almost concealed by overhanging hypertrophied mucosal folds. The floor lay well below the level of the muscularis mucosae which was missing. It was composed of granulation tissue bathed with pus. Lying in the floor was a large thrombosed artery, which had lost by erosion the superficial portion of its wall. In the vicinity of the larger ulcer the submucosa was fibrotic, heavily invaded by inflammatory cells. Plasma cells and eosinophils were numerous and lymphocytic follicles were especially prominent. Other arteries, possibly branches of the eroded artery, showed proliferative intimal thickening. The principal histological findings have been previously related.

Case 4. F. B., white, male, aged 35. The patient entered the Clinics June, 1938, with a history of non-specific ulcerative colitis in 1926 and with healing in 1928. For six months prior to admission, he complained to a vague "hollow burning ache" in the upper abdomen not relieved by alkalis. During this period he also noted the gradual onset of peripheral edema which did not disappear on bed rest. The physical findings were essentially normal with the exception of the peripheral edema.

Laboratory findings. Blood and urine analyses were within normal limits; the total plasma proteins were 4.98 with an A/G ratio of 1.74; gastric analysis revealed 10 clinical units of free acid with histamine stimulation.

X-ray examination (F. E. T., June 28, 1938). "Immediately below the cardiac orifice the stomach appeared narrow and the rugae almost completely destroyed. This appearance involved almost the entire body of the stomach. When the stomach was filled complete narrowing in the mid-portion was spectacularly shown, but instead of having the usual stiffness present in most carcinomas, the stomach appeared to be somewhat soft and pliable. Peristalsis did not pass through the body of the stomach but was quite active in the distal 5-6 cm. of the antrum. The impression of a soft infiltrating carcinoma involving the entire stomach except for a small amount of the extreme upper portion of the cardia and the distal portion of the antrum was obtained."

Gastroscopy (June 28, 1939, R. S.)—"Outspoken changes were seen in the greater curvature, anterior wall and lesser curvature of the body. A huge tumor of a peculiar structure was noted. It consisted of many spongy nodules and folds separated from one another by small dark creases. Many pits and dark depressions were observed and it was impossible to tell whether or not they were small ulcerations. A rather sharp limitation toward approximately normal mucosa was found only at the upper edge of the lesser curvature but even at that point, there was no abrupt wall. At the greater curvature all the folds appeared to be infiltrated, dark red and nodular and the tumor seemed to infiltrate diffusely.

Impression: Although carcinoma is the most likely diagnosis the spongy soft appearance of the tumor is unusual. The nodular stiff folds of the greater curvature resembled a case of lymphoblastoma."

The patient died in April, 1939, from a riding embolus of the aortic bifurcation.

The preserved stomach³ was definitely enlarged. The mucosal folds resembling convolutions of the cerebrum, were more numerous and of greater size than seen in the usual stomach, and extended from the cardia into the antrum three to five centimeters from the pyloric sphincter.

The microscopic sections revealed obvious thickening of the mucosa, but little increased thickness of the muscular coats. The increase in epithelial thickness resulted from elongation and hypertrophy of the mucous portion of the glands. In many portions the entire gland was converted into a simple mucous crypt. In other regions acid-secreting and pepsinogenic cells persist in short segments in the basal portion of the glands. This was true both in the pyloric antrum and in the body of the stomach. Where the basal portions of the glands were preserved in the latter region parietal cells were scanty. Cystic transformations of the mucous glands were numerous with marked deformation of the adjacent non-cystic glands. Many glandular lumina were filled with retained secretions, and others contained exudate. Focal interstitial reactions consisted chiefly of plasma cells and there were regions where large hyaline inclusions filled greatly altered plasma cells (Russell's bodies). It is noteworthy that these changes while present in multiple sections of the pylorus and body, were absent in sections close to the cardiac orifice. Here the glands had a more normal structure.

Case 5. A thirty three year old house wife had been followed in the clinic for 5 years with two deliveries, a ruptured appendix complicated by a subdiaphragmatic abscess, varicose veins and schizophrenia which had been treated with shock therapy. On April 15, 1943, she was seen with complaints of right upper quadrant pain, sharp or aching in character, brought on by taking food, post prandial distention, nausea and occasional vomiting. Epidodes of jaundice, pruritis and intermittent clay colored stools had been noted during the past 12 years. Physical examination was normal except for marked tenderness in the right upper quadrant. No abdominal masses were palpated.

The laboratory findings disclosed; normal urinalysis; red blood cells, 3,760,000 per

³ Kindness of Dr. Libby Pulsifer, Rochester, New York.

cm.; hemoglobin 11.5 gm.; white blood cells, 7,250 per cm. and the differential normal while the histamine test showed no free acid in eight samples. A diagnosis of gastric polyposis was made by x-ray. A previous gastric x-ray March 31, 1939, was reported as suggestive of gastric polyps. Gastroscopic examination (J. B. K.) demonstrated a normal pylorus and pyloric activity. Most striking were the numerous polyps seen from the angulus to the cardia, literally "peppering" the gastric mucosa everywhere. The surfaces of the polyps were smooth and covered with adherent patches of mucus. No evidence of malignant change was detected but the gastric mucosa everywhere was thinned and greyish pink, and numerous blood vessels were seen; on the posterior wall at depth II numerous small hemorrhages were noted.

At operation on April 1, 1943, Dr. W. E. Adams found the abdominal viscera, except the stomach normal. In the mid-portion of the stomach numerous polypi were palpable. A mid-portion partial gastrectomy was done, leaving only a sleeve of cardia and pyloric antrum for anastomosis. Visual and manual inspection of the remaining stomach revealed no polyps.

The gross and histologic findings have been previously recorded.

The patient was seen three months after discharge and in May, 1945, each time without gastric complaints, and maintaining weight, eating well.

Case 6 (15). H. B., white, female, aged 49 years. The patient entered the Clinics in October, 1939, with a 10 year history of epigastric burning and belching partially relieved by alkalis and bland diet. The family history was pertinent in that a sister had been operated on for benign gastric polyposis 27 years before, at the age of 24, and the mother had died of a colon malignancy. The physical examination was non-contributory. Free HCl was present in the gastric fluid. There was no occult blood in the stools. Blood and urine studies were normal.

X-ray examination of the stomach at the Ford Hospital in September, 1939, revealed an irregularity of the lesser curvature. Gastroscopy at that institution revealed a "mucosa thrown into heavy folds presenting a dark red appearance with several heaped up apparently polypoid areas without evidence of bleeding or ulceration. This occupied a portion of the cardiac end of the stomach.

Gastroscopically (October 13, 1939, R. S.) "Some folds of the greater curvature and the posterior wall were only 2-4 cm. in length, branching but completely stiff, beady and nodular. In the cardiac portion a huge fold like protrusion was observed, entirely stiff and infiltrated with many nodes on its surface, hemorrhages in its mucosa and a tendency to bleed easily. The impression of severe hypertrophic hemorrhagic gastritis was gained and reexamination was advised.

At the second gastroscopy (R. S., November 15th) "The beady stiff folds of the anterior wall were well seen and the tumor like protrusion of the cardia was visualized. There were no sharp limiting edges of this stiff protrusion, which contained irregular nodes and one hemorrhage. No ulceration was present. Tumor forming gastritis was thought likely with carcinoma second possibility."

On November 29th "The tumor like prominence of the upper posterior wall was again noted with no essential change."

At operation on November 30th, by Dr. Brunschwig, the mucosa of the fundic portion was found to be extremely hypertrophic, thrown up into numerous great folds, which resembled gross papillomatous structures. In two or three places there were true papillomata with narrow stalks and cauliflower-like tops. These varied in size from pea to marble. The stalks of these papillomata were extremely friable. The papillomata were removed and a segment of gastric mucosa in the region of the marked hypertrophy excised for study. Histologically the papillomata proved to be hyperplastic rather than adenomatous and associated with a hypertrophic (severe) gastritis.

The gross features were, similar to those of the stomach of Case 5, while the microscopic findings were like those of the hypertrophied folds of Cases 1 and 2. The main point of difference between these hyperplastic polyps and the redundant folds of Cases 1 and 2 was the greater abundance of exudate interstitially and in the glands of former.

An x-ray examination April 11, 1940, again showed the unusually large rather soft folds in the body. There was a persistent collection of barium along the greater curvature which looked like crater although the possibility of barium caught between the folds was considered. No polyps could be demonstrated.

At the fourth gastroscopy March 11, 1940 (R. S.) "The folds of the posterior wall of the mid-portion were definitely swollen and partly covered by small granules. The upper part of the posterior wall were swollen, but not stiff (not appearing tumor like)—slight bleeding was present. No scars were seen."

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THE EFFECT OF VAGOTOMY ON GASTRIC FUNCTION

STEWART WOLF,* M.D., AND WILLIAM DEWITT ANDRUS, M.D.¹

INTRODUCTION

It has been suggested as the result of previous work (1) that the vagus nerve may be implicated in the mechanism of production of a potentially destructive condition in the stomach of man. This state is characterized by hyperemia, hypermotility and hypersecretion of acid, and associated with fragility of the membrane and a lowering of pain threshold. In fact, in 1924 Stahnke (2) in cats, and later Manning, Hall and Banting in dogs, were able, by prolonged vagus stimulation, experimentally to induce peptic ulceration (3). The above body of evidence led to the development of the surgical procedure of bilateral supradiaphragmatic section of the vagus nerves in man as a therapeutic device in peptic ulcer. Thus far, eighteen months after the introduction of the procedure by Dragstedt (4), the clinical results appear to be satisfactory. As reported by numerous investigators (5, 6, 7) vagotomy is followed by a prolonged reduction in acid secretion and motility in the stomach, alleviation of symptoms, and in most cases healing of the ulcer.

Opportunity has recently been afforded to study experimentally an individual without peptic ulcer who was subjected to gastrostomy followed by bilateral section of vagus nerves incident to an attempt at removal of a carcinoma of the esophagus at the level of the aortic arch. Observations were made on the stomach of this subject before and after section of the vagus nerves. It was necessary to accomplish direct examination of the gastric mucosa with a Brown-Buerger cystoscope because the gastrostomy opening was only 1 cm. in diameter. Otherwise data concerning gastric function were obtained after the manner previously reported (1).

The subject was a 58 year old skilled laborer of German extraction. He was a polite, soft spoken individual, with a slightly suspicious attitude. Married at the age of 38 he had lived the quiet life of a conservative family man. He had 2 children, one of whom died in early childhood of pneumonia. Of recent years his wife had apparently tired of the quiet sober existence of their household and had sought the company of other men. He had discovered her infidelity, however, only when she deserted him a month prior to his admission to the hospital. This coincided approximately with the onset of his esophageal symptoms. He noted progressive difficulty in swallowing associated with listlessness, despondency, anorexia, weight loss and difficulty in concentration.

* Hofheimer Fellow in Medicine.

¹ From the New York Hospital and the Departments of Medicine and Surgery, Cornell University Medical College, New York, N. Y.

In the hospital, after the diagnosis of carcinoma of the esophagus was established, a Glassman gastrostomy was performed preliminary to the attempted removal of the esophageal neoplasm.

OBSERVATIONS BEFORE VAGOTOMY

1st Observation. The stoma, midway between the umbilicus and xiphoid and slightly to the left of the midline, was entered with a cystoscope. The membrane appeared moderately pale (45 Tallquist units) and the rugae not remarkable.

The pattern of motor activity was normal. Gastric juice obtained throughout a 2 hour period amounted to 52 cc. It was bile stained, extremely viscous, contained no free acid and only 15 units of total acid.

Sensory Examination. Tactile stimulation with a blunt glass rod was not felt.

Temperature. Water was quickly introduced into the stoma through a tube with a 1 mm. lumen and a 2 mm. wall. When 10 cc. of water at 40° C. was introduced, a sensation of warmth was felt, just below and slightly to the left of the umbilical region within 7 seconds. Fifteen cc. of water at 13½°C. was felt as cool in the same area within 15 seconds.

Pressure. Using a blunt glass rod 5 mm. in diameter, the patient was able to recognize a sensation of pressure and approximately localize it when a pressure of approximately 40 gm./sq. cm. was exerted.

Pain. Pressure of 125 gm./sq. cm. with the blunt glass rod induced a slight aching pain. When this pressure was sustained for 30 seconds nausea ensued with associated salivation. Removal of the glass rod resulted in prompt disappearance of the pain, but nausea persisted for 30 seconds thereafter.

2nd Observation. At the time of the second experimental period 2 days after the first, the patient's appearance and behavior were essentially as before. He was polite and cooperative but appeared grave and taciturn. The mucous membrane was examined as before and found to be 50 on the scale, somewhat redder than at the time of the previous experiment. Eight and one-half cc. of viscous, white gastric juice were obtained with a free acid of 0 and total acid of 10. While the membrane was under observation a discussion of the subject's illness was entered upon. He said that he had been frightened and depressed about his illness and was not particularly optimistic for the future. The topic was then switched to his wife who had recently deserted him, after 20 years of married life. He said that he still loved her, that they had been happy but that he did not make enough money for her and that her economic demands had become greater and greater in recent years. He spoke of this and of her infidelity in a quiet monotonous voice. His feelings were obviously those of dejection and defeat. The gastric mucosa became paler, or less than

40 on the scale. During the 45 minutes of discussion, 22 cc. of gastric juice were removed which yielded free acid of 0 and total of 10 units. Bile appeared in the specimens but no nausea was noted. Much less motor activity occurred at this time than on the previous experimental day.

Following the interview an experiment with prostigmine bromide, was carried out. It is noteworthy that gastric hyperemia of moderate degree associated with accelerated motor activity occurred following injection of the drug although there was still no detectable change in acid secretion.

3rd Observation. On coming to the laboratory for the third time and still prior to vagotomy a marked change in the appearance and manner of the subject was noted. He was less taciturn and reserved. His face was red and he appeared somewhat exasperated and irritable. He complained of stiffness and back pain ever since the previous experiment and confessed that he was angry at having to come down to the laboratory again in view of the apparent delay occasioned in his operation.

His stomach was examined and found to be much more hyperemic and engorged than before, about 70 on the scale. He was more voluble and talkative. Asked about his concern regarding his condition, he said that he was reminded of the first doctor whom he had consulted for difficulty in swallowing. The latter had focused his attention on the stomach much to the annoyance of the patient. "He was so dumb; I told him it wasn't in my stomach, because I knew I couldn't swallow right. He made me waste four weeks fooling around". On this occasion there occurred much more spontaneous motor activity in the stomach but acidity values were approximately the same as before—free acid 0 and total acid 15. The mucous membrane was so turgid, however, that the minor traumata incident to the instrumentation with the cystoscope caused bleeding.

Comment: The subject's dominant mood during this interview was anger coupled with hostility and strong feelings of frustration. His stomach displayed the picture of hyperactivity so characteristically found in the subject, Tom, during situational conflicts productive of aggressive attitudes (1).

OBSERVATIONS FOLLOWING VAGOTOMY

Following operation the patient's convalescence was uneventful. The attempt to remove the esophageal tumor had been unsuccessful but bilateral vagotomy was accomplished. The patient was not dissuaded from his belief that his operation had been a success and that he would soon be able to eat normally. His attitude and bearing were noticeably more cheerful and optimistic than before.

1st Observation, 17 Days After Vagotomy. The cystoscope was introduced as before. The membrane appeared pale, 40 on the scale, and the rugae seemed

thinner than on any of the examinations prior to vagotomy. During this and two subsequent experimental periods lasting 2 hours each, 19 and 21 days following vagotomy, no spontaneous waves of forceful gastric contractions were recorded. On this first occasion 45 cc. of gastric juice containing food remnants and fat globules were recovered despite the subject's not having received a feeding for 13 hours prior to examination. The fluid was brownish in color and had a fetid odor. Free acid measured 0 and total acid 25.

Sensory Examination. Tests for touch and temperature, pressure sensation and pain yielded results essentially similar to those reported in experiments done before vagotomy. As before, sustained painful pressure on the stomach with a glass rod resulted in nausea.

2nd Observation. The patient had been fed four hours prior to the second experimental period following vagotomy. Ninety cc. of liquid gruel was recovered containing recognizable food particles and fat globules. The mucosa was examined and the color found to be 55, considerably redder than at the time of his previous examination. Prostigmine bromide was then administered as before. The membrane became slightly redder, 60, one hour after injection of the prostigmine and slight motor activity was induced. The rugae thickened slightly but did not appear significantly engorged.

Comment: It would appear that prostigmine while primarily a potentiator of the effects of acetylcholine, also exerts by itself some slight acetylcholine-like action. Such an action has already been recognized in the skeletal muscle by Riker and Wescoe (8).

3rd Observation. On the third experimental occasion following vagotomy the patient's stomach contained fluid similar to that on the first occasion. Free acid was 0 and total 15. The membrane was pale, 40, and the folds appeared especially thin. After the baseline observations had been made an attempt was made, as before, to induce anger and resentment in the subject by discussion of the doctor who had failed to diagnose his condition when he first consulted him. As on the occasion prior to vagotomy he appeared to become significantly angered with flushing of the face, loud voice and aggressive gestures. "I only went to him because he is around the corner. He said the lining was off my stomach and gave me some stuff that made me feel lousy . . . Last winter I had some crushed toes. He messed them up, too. He charged me enough—\$8.00 a treatment. I'll tell him off." During this outburst the patient's stomach was continuously under observation through the cystoscope but despite the redness of his face, there occurred no detectable change in the appearance of his gastric mucosa.

Comment: Failure of the stomach to become engorged during such a state does not necessarily implicate the vagus as a route by which impulses responsible for gastric hyperfunction occurring in response to situational threats reach the stomach. The evidence is highly suggestive, however, especially

when considered in company with the clinical results of the treatment of peptic ulcer by vagotomy.

SUMMARY

In experiments on a second subject with a gastric fistula certain findings previously observed in Tom (1) have been confirmed. The first series of observations was carried out prior to bilateral section of the vagus nerves. These were followed by a similar series after vagotomy. With regard to the sensibility of the stomach, it was found that tactile stimuli were not felt, but pressure and pain sensations could be elicited by appropriate stimulation of the stomach with a blunt glass rod. When such painful stimuli were prolonged, nausea ensued. The gastric mucosa was also found sensitive to heat and cold stimuli. The sensibility of the stomach, as determined by these tests, was not altered by vagotomy.

The relative redness of the gastric mucosa changed from time to time and these changes in color were paralleled by changes in turgidity of the membrane. Vigorous motor activity regularly accompanied hyperemia in this subject's stomach as in Tom's. Acid production in this subject appeared to be impaired, however, and a high acidity was not found in company with hyperemia. Following vagotomy the membrane was usually pale and no spontaneous motor activity was recorded. Mild hyperemia and engorgement of the mucosa following ingestion of a meal was observed, however, after vagotomy. Injection of prostigmine prior to vagotomy resulted in marked acceleration of motor activity and hyperemia of the mucosa without increase acid secretion. After vagotomy these effects were slight but still observable.

This subject's dominant mood was depressive and, as in the case of Tom, it was found that discussion of depressing topics resulted in a pallor of the mucosa with diminution of motor activity. It was possible, however, with reference to appropriate topics, to induce feelings of anger and resentment in the subject. These feelings were associated prior to vagotomy, with gastric hyperemia, engorgement and hypermotility, but, as with other stimuli, no increased acidity. After vagotomy, although anger and resentment were successfully aroused, no observable changes in gastric function occurred.

CONCLUSIONS

1. Certain inferences reported in earlier studies regarding the sensibility of the normal human stomach have been confirmed.
2. Other inferences regarding the association of gastric function with life situation and emotional state have also been confirmed.
3. Pallor and hypomotility of the stomach were observed 3 weeks after bilateral section of the vagus nerves.
4. Afferent fibres subserving pressure sensation, heat and cold, pain and

nausea are not interrupted when both vagus nerves are sectioned above the diaphragm.

5. The vagi are not essential to the occurrence of gastric hyperemia which follows the ingestion of a meal.

6. Evidence has been adduced which indicates that the vagus nerves carry the efferent impulses concerned in the production of gastric hyperfunction in reaction to certain threatening life situations.

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THE RATE OF HEALING OF GASTRIC ULCERS^{1,2}

H. MARVIN POLLARD, M.D., WILLIAM H. BACHRACH, M.D., AND MALCOLM BLOCK, M.D.

INTRODUCTION

Cummins, Grossman and Ivy (1) reviewed the literature on the rate of healing of peptic ulcer and concluded that there was a paucity of clinical studies of this important phase of the ulcer problem. The authors then presented observations in their own series of sixty-three duodenal and six gastric ulcers. The average healing time as judged by disappearance of the craters on x-ray examination was thirty-seven days for duodenal and forty-two days for gastric ulcer. No correlation was found between the healing time and the size of the craters, age, recurrence, or duration of symptoms.

The above series deals primarily with duodenal ulcers, and includes so few gastric ulcers as to render the figure for the average healing rate of these lesions open to question. For example, it is clear from work in animals that gastric ulcers heal on the average more rapidly than ulcers of the upper intestine (2). We have examined our records on cases of gastric ulcer in an effort to obtain a more reliable estimate of the rate of healing than has hitherto been available.

MATERIAL AND FINDINGS

One hundred consecutive "tests of healing" of gastric ulcers were collected from the case records of the University of Michigan Hospital. The cases were classified into three groups.

(1) Sixteen persons were treated as out-patients; the time of the first follow-up x-ray varied from twenty to sixty-three days after the beginning of treatment, so only a very crude estimate of the time of disappearance of the ulcer in these cases can be made. In eight cases, a follow-up was obtained within thirty-five days; five were found to be healed, the earliest being healed at twenty-seven days. Of the remaining three cases, two were not yet healed at fifty-two days and one hundred and eleven days respectively and in the third no further follow-up was obtained, so in these latter three cases there is no proof that the lesion was benign.

If we extend the checkup interval on these out-patients to forty-five days, we find that eleven patients are included, of whom eight were healed; the same three patients as noted above comprise the unhealed cases. In summary then, it appears that remission of a gastric ulcer *may* be obtained with out-patient treatment sometime within four or five weeks.

¹ From the Department of Internal Medicine, University Hospital, University of Michigan, Ann Arbor, Michigan.

² This study was made possible by a grant from the Earhart Foundation.

(2) Fifty-one patients were treated in the hospital and were either discharged when the follow-up x-ray showed reduction in size, but not disappearance, of the ulcer, or were operated upon because the lesion did not regress.

In the ten patients operated upon immediately following the "test of healing" a benign ulcer was found. Six discharged patients returned later for surgery and proved to have benign lesions, making a total of sixteen cases that came to surgery.

In twenty-two cases the lesion was found to be healed on a subsequent follow-up in the out-patient department. In thirteen cases the ulcers were not known to have healed and were, therefore, not proven benign. Thus, there were thirty-eight benign gastric ulcers which failed to heal under hospital treatment in a period ranging from eight to forty days, or an average of twenty-three days.

(3) Thirty-three patients were treated in the hospital until a negative x-ray was obtained. The period of treatment up to the time of x-ray evidence of disappearance of the lesion ranged from ten to fifty days, or an average of twenty-five days. A comparison of this group with the thirty-eight hospital-treated cases reasonably shown to be benign appears to indicate that patients with gastric ulcer, treated in a hospital for four weeks, have about a forty-five per cent chance of being healed sometime within that period.

We then went further back in the records to obtain additional cases of gastric ulcer healing before discharge from the hospital. A total of forty-six healing episodes in forty-three patients was tabulated and analyzed to determine what factors, if any, affected the rate of healing within this group. We could find no significant effect in relation to 1) sex, 2) age, 3) time since the first onset of ulcer symptoms, 4) number of previous recurrences, 5) type of treatment, 6) presence of associated duodenal ulcer or deformity, 7) maximal acidity after histamine, or 8) concomitant cardiovascular disease (hypertension and/or arteriosclerosis).

There was some suggestion that healing was retarded in the presence of anemia, but this needs further investigation because our figures may reflect only a policy of delaying the x-ray follow-up in patients with significant bleeding. An apparent delay in healing of the larger lesions also awaits further observation, since the size of the ulcer was noted in only seventeen cases.

The question arises whether there was any difference between the group that healed while in the hospital (average twenty-five days) and the group which did not heal in a comparable period of time (average twenty-three days of hospital treatment to follow-up x-ray). A preliminary survey of the possible factors concerned yields only the following information that is possibly suggestive of a significant difference: Among the thirty-four healed cases in whom a histamine gastric analysis was recorded, there were twelve per cent who had a maximum acidity of ten units or less; in the unhealed group no patients had

a maximal acidity within this low range. Among the healed patients eight per cent had a maximal acidity of more than seventy-five units, whereas in the thirty-three unhealed patients in whom gastric analyses were done, twenty-seven per cent had a maximal acidity of more than seventy-five degrees. The average maximal free acidity in the group of healed patients was thirty-nine degrees as compared with fifty-five in the unhealed group. It must be emphasized that these figures were taken from routine fractional analyses done on the hospital wards.

An examination of the material presented strengthens our conviction that any useful average figure for the healing of gastric ulcers will be obtainable only by a planned study designed to follow carefully the progress of the ulcer so that the actual time of disappearance of the lesion may be known within one or two days. Such an investigation is now in progress.

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SYNDROME OF NON TROPICAL SPRUE WITH HITHERTO UNDESCRIBED LESIONS OF THE INTESTINE

JOSEPH SCHEIN, M.D.¹

From the Laboratories of The Mount Sinai Hospital, Department of Pathology, New York, N. Y.

INTRODUCTION

Because, traditionally, pathologists have been trained to think largely in anatomical terms, those investigating sprue in the early years of this century paid attention mainly to those cases showing atrophic and ulcerative intestinal changes. Nevertheless, it became apparent, as time passed, that there existed no generally valid correlation between the morphologic findings and the clinical picture as observed in the tropics. As physicians grew more aware of the condition, the tropical syndrome proved to be somewhat different from that observed in the temperate zones, where it became increasingly more possible to establish a definite cause for the patients' illness at necropsy. However, there are many cases diagnosed as non-tropical sprue, in which no lesions are found at post-mortem examination.

The purpose of this report is to call attention to the fact that, under favorable circumstances, it is sometimes possible to find a microscopic anatomic basis for those cases of "idiopathic" sprue where no gross lesions, obviously capable of interfering with intestinal resorption, can be found at the autopsy table. Naturally I exclude now the well-known types of sprue syndrome secondary to abdominal Hodgkin's, tuberculosis (36), or other disease of the lymph-nodes and, indeed, all diseases in which there is interference with the pathways for absorption from the gut, either at the mucosal surfaces or in the lymph channels or portal radicles. The morbid anatomical changes could therefore range from extensive atrophy of the small intestine, or even in rare cases of extensive resection of the small bowel, from simple absence of adequate absorbing surface to the more obvious mechanical factors such as are mentioned above. With simple atrophy there will have to be some doubt, because of a suspicion that the changes observed might be due simply to post-mortem change or to chronic wasting disease.

If, on going through the literature on sprue, one limits oneself to a study of those cases in which there was no obvious lesion, then one is left with cases in which only small microscopic changes were found that were inconstant, and, in some instances, not convincing. In many, no alterations were noted.

Actually most of the cases reported were observed in the tropics, and they had certain features such as a good response to dietotherapy, or the presence

¹ Emanuel Libman Fellow in Pathology.

of a macrocytic, hyperchromic type of anemia, or a lack of any tendency to the hypocalcemic tetany and osteomalacia which are seen in the non-tropical variety. The increased total fat and fatty acid content of the stools constitutes a similarity in both conditions, and hence it is fair to make some use of the anatomical observations that have been made in the cases of tropical sprue.

The small-intestinal findings in sprue are logically the chief points of interest. Thin (77), and Wethered (88) found atrophic changes in the small intestine but the latter viewed these with some well-founded skepticism and thought them due mainly to post-mortem changes. Faber (13) and Justi (39) described ulcerations with secondary widespread destruction of the villi. Justi reported that the villus structure was short and swollen, that the free one-half of the stroma contained many chronic inflammatory cells, and that the core of the villus was filled with very fibrillar cellular connective tissue. Beneke (4) however, did not agree with these findings, and felt that marked inflammatory changes were not present. Faber, Van Der Scheer, Thaysen (76) and Mackie (48) found no such alterations, although the latter spoke of the "withering of the villus". Manson-Bahr (50) considered the villi atrophic from proliferation of fibrous connective tissue, and thought similar changes were present in the submucosa. He reported also that the mucosa was diffusely infiltrated with round cells.

In 1922, Fisher and Von Hecker (18) described sprue in a patient who had lived the major part of his life in East Asia and Java where he had had many intermittent enteric illnesses over a period of 17 years. One attack in 1902 was diagnosed as cholera and another in 1913 as dysentery. During the latter attack he had an operation for "perforation of the intestines." In 1917, he had chronic diarrhea without blood or mucus for one year. Following a period of health for two years he developed the characteristic intestinal picture of sprue from which he died two years later.

The pertinent findings were confined to the alimentary tract. The mucosa of the tongue and esophagus were somewhat atrophied. Shortly below the beginning of the esophagus there was a pinhead size mucosal ulceration with chronic inflammatory reaction. In both organs there were abundant macrophages in the subepithelial connective tissue filled with yellow brown pigment. This, identified as lipofuscin, was especially striking in the musculature of the entire small and large intestines, although it was likewise present in the stratum proprium. The stomach showed similar pigmentary changes. The small intestine showed not the slightest trace of atrophy, nor was the submucosa infiltrated. In the mucosa of the lower part of the jejunum, and throughout the ileum there were small, flat, lentil sized ulcerations going through to the longitudinal musculature. In the cecum there were 20 small pinhead-size discolored areas in whose vicinity the mucosa was perhaps somewhat atrophied.

In general, the authors considered mucosal and submucosal round cell infiltrations to be present in the colon. In this, they differed from Justi, Van Der Scheer, Mackie, and Thaysen. The liver was not remarkable. In view of the complicated sequence of intestinal ailments extending over many years, I think it would be unwise to regard these findings as bearing directly on the development of the sprue syndrome. The pigment-filled cells may well have represented an unusual type of degenerative change secondary to chronic enteritis or malnutrition, especially in respect to Vitamin E deficiency.

In 1924 Manson-Bahr (51), who considered the above an acute case of sprue, and felt therefore that the mucosal lesions were primary, came to the conclusion that the essential lesion of sprue was an ulceration of the small bowel affecting chiefly the lower end of the ileum. He too described pigment (hemo-fuscin) in the endothelial leukocytes of the muscularis mucosae. In 1929, Mackie and Fairley (48) studied thoroughly 8 cases of sprue, and decided that the earliest changes were in the villi where there was infiltration with small round cells and a degeneration of the epithelial covering. Some congestion was noted, but signs of active inflammation or infiltration with polymorphonuclear leukocytes were absent. Essentially, they considered the process a degenerative and non-inflammatory one, the end stage being a shrunken and acellular villus. Most of the changes were in the ileum, and, although occasionally ulcerations without inflammatory reactions were seen, no scars were observed. Eventually, though not early, the glands of Lieberkuhn underwent degenerative changes. In half their cases, they noted an atrophic thinning of the gut wall. They felt that bacterial invasion of the mucous and submucous layers was a rather common phenomenon. The liver, as in nearly all reports, was decreased in size. These authors admittedly made their observations in the hot climate of Bombay where no adequate refrigeration facilities were available. Nevertheless, they took confidence in them on the basis of a control study on one normal monkey, done under similar circumstances by Mackie (49) in order to rule out post-mortem changes.

In his comprehensive review on sprue in 1932, Thaysen (76) came to the conclusion that chronic inflammation was as inconstant as ulceration, and stressed emphatically his belief that in well-preserved autopsy material no degenerative or atrophic changes could be found in the epithelium of the villi outside the actual areas of ulceration, whenever present, and that only in the submucosal connective tissue could alterations be found. This review included 14 autopsied cases of tropical sprue and 34 cases of non-tropical sprue from the literature. But in only 6 of the latter were there autopsy findings to be analyzed, and in one of these there was no histologic description of the intestines. The small bowel sections showed in 1 case a thin, loose, edematous submucosa, a somewhat atrophic mucous membrane, prominent lymphoid follicles, and

considerably enlarged mesenteric nodes, described as highly edematous. In 1 other case, where there were no significant findings mentioned in the intestines, mesenteric lymph gland hyperplasia was reported. It is of interest to note, however, that this patient suffered from caseous bilateral pulmonary tuberculosis. In a third case, the intestines were likewise described as negative, but here too, pulmonary tuberculosis was present. This is emphasized because the importance of amyloid changes, not uncommon in tuberculosis, for the development of a sprue syndrome will receive comment later. The fourth case showed several acute ulcerations with perforation as well as subacute and chronic ulceration with scar formation, but these findings were discounted by the original author, Rosendahl, because of the heavy x-ray treatment the patient had undergone for breast tumor. A fifth case revealed no alterations. All in all, Thaysen concluded that, because of the variability of the anatomical lesion in the sprue syndrome and the long average duration of the disease, the changes described were probably secondary to invasion by non-specific microorganisms of relatively low virulence or secondary perhaps to mucosal irritation by an abnormally acid intestinal content.

In 1934, Dunner, Hirschfeld and Gerald (12) described 2 cases of non-tropical sprue in neither of which were there significant intestinal lesions. The liver, however, of one of these was characterized as "chronic atrophy with subacute exacerbations."

In 1937, Rosenthal (64) reported 3 cases of non-tropical sprue presenting the picture of fatty diarrhea which at autopsy showed striking anatomical changes. One showed many lentil-sized ulcerations in the mid-small intestine and a thickened infiltrated mucosa, with scar formation, in the ileum. The colon, likewise, showed chronic inflammatory changes. Essentially similar findings, varying in intensity, however, from acute perforating ulcerations to chronic stenosing scars of the small intestine and polypoid hyperplasia of the large intestine were present in the other two. All three, therefore, were cases of chronic ulcerating enterocolitis, of undetermined etiology. These were apparently not studied bacteriologically. In the same year, Fairley and Mackie (14) reported 4 cases of the sprue syndrome secondary to mesenteric lymphadenopathy of various types. Although laparotomy in a patient, later shown to have mesenteric Hodgkin's disease, revealed marked distension of the small intestinal lymphatics and adherent loops of ileum, an autopsy was made in only one other case. Except for hyperplastic lymph nodes, there were no significant findings in the abdominal cavity. A slight atrophy of the small intestine was attributed to the general wasting. Microscopically, some thickening and increased fibrosis of the submucosal layer of the descending colon was present.

In 1938, Hotz and Rohr (33) found small-intestinal changes in only 1 of 22

cases of non-tropical sprue. These consisted of atrophy and ulcerations, not further described. They cited, however, the experience of Uehlinger (78) who in 6 cases of celiac disease, found varying amounts of fat in droplets at the domes of the villus tips, indicating that some fat resorption was going on, even in the severest cases of Gee-Herter's disease. In the light of present knowledge, it may justly be criticized that this group is a very heterogeneous one. Nevertheless, some of the cases pose problems similar to those in undoubted sprue, and therefore this deserves mention. None of the liver findings were remarkable. That same year, Glynn and Rosenheim (20), describing a case of the sprue syndrome in association with mesenteric chyladenectasis, reported atrophy of the small intestinal mucosa and Peyer's patches, a generally thickened serosa, and a duodenum that was characterized as rubbery. This bore great resemblance to the classical case ending with a picture of steatorrhea that was reported by Whipple (89) in 1907. Besides the well-known remarkable findings in the mesenteric lymph nodes, Whipple described the mucosal epithelium as normal, the small intestinal villi "enlarged" and the submucosa "thick", the latter two the result of fat deposition and giant-cell reaction. Vaux (79) found in a case presenting a similar syndrome and associated with similar lymphadenopathy a jejunum in which the villi and the lymphatics were markedly dilated, and in which the stroma contained many fat-laden macrophages. In a case of sprue with an old gastrojejunostomy a complete autopsy by Burgdorf and Barry (8) revealed no intestinal changes.

In 1939 (25, 26), in discussing the sprue syndrome, Hanes laid little stress on the morbid anatomy, but mentioned that gastroscopic observations revealed definite atrophy in 8 out of 20 cases. He likewise considered the possibility that deficient storage by the liver of some factor might produce the picture of sprue. In the same year, Jeckeln (38) described the pathologic findings in 3 cases of the sprue syndrome. In only one of these were there unequivocal changes, a widespread hypertrophy of the reticulum of the intestinal villi, a microscopic alteration which could account for the outspoken clinical picture. Such changes could fit in with the opinion of Markoff (54) who felt on clinical grounds that this disease was secondary to a chronic gastroenteritis. A most interesting association of steatorrhea with severe giardial infestation was reported in 1940 by McGrath, O'Farrell, and Boland (57) under the title of "Giardial Steatorrhea." They found dilatation and denudation of the upper part of the small intestine, with ulceration of the mid-ileum whose lumen was somewhat constricted. They state there was no involvement of the submucosa layers. The theory of intestinal disturbance due to injury to the intrinsic nerve supply, as suggested by Hurst (35), has as yet received no convincing anatomic support. Nevertheless, investigation along this line might well be profitable. In 1943, Barker (3), reviewing the subject,

cited Napier who stressed the oft-found atrophic wasting of the intestinal layers.

Aside from attempts to implicate many other anatomical factors as being of pathologic significance, such as primary pancreatic (16,17) or liver disease, the parathyroids (66), the adrenal cortex (80, 81, 82, 83, 84, 85, 11, 71), and even the constitutional make-up, the intestinal changes in general have naturally attracted the most attention, and those above are the salient positive ones which can be combed from the extensive but unrevealing literature on this subject. Those cases which are labelled non-tropical sprue are essentially those, with few and not well-defined clinical differences from the tropical variety, which occur among residents of the temperate and northern zones, and which, aside from the gross exceptions previously mentioned, show for the most part an absence of convincing anatomical changes. Occasionally, however, changes are found which may logically be regarded as responsible for the sprue syndrome. The following case demonstrates such lesions.

CASE REPORT

This was the second admission of a 15 year old school boy to The Mount Sinai Hospital. He was first here in November of 1943 with a chief complaint of vomiting, abdominal pain, and diarrhea, and an 18 pound weight loss during the preceding 3 months. His past medical history was apparently non-contributory except for a herniorrhaphy with an uneventful course about one year before. He had been in good health until August of 1943, when he suddenly lost appetite, complained of having a "bad taste in his mouth," and had malaise generally, very much as in "grippe." One week later he began to have very loose bowel movements. The stool became persistently grayish-yellow and bulky. He vomited once every 2-3 days, and brought up much undigested food. These bouts were accompanied by midabdominal cramps and pain; occasionally his breath had a fecal odor. He was sent to another hospital where he received sulfasuxadine, liver and vitamins for one month before his admission to the surgical service of The Mount Sinai Hospital. His symptoms, however, progressed slowly and of necessity, his dietary intake became very poor.

Physical examination revealed that he had a temperature of 100° which was present, however, for only one day, asthenia, slight cyanosis of nail beds, and a generalized lymphadenopathy characterized by slightly enlarged, non-tender, movable nodes. He also had a dry, loose skin which was described as being tan, "rough" and showing "follicular hyperkeratosis," (characteristic of vitamin A deficiency) without mucosal pigmentation. A tentative diagnosis of incomplete intestinal obstruction was made, due probably to diffuse jejuno-ileitis or lymphosarcoma of the retroperitoneal nodes, or possibly of non-tropical sprue of undetermined pathogenesis.

The hemoglobin was 89%, and the white blood cells 10,650, with a differential showing 22% polynuclears, and 68% lymphocytes. His red cells were 5,000,000.

No sulfa crystals were found in the urine. Stools were guaiac negative. There was plentiful free acid in the gastric contents. Blood urea nitrogen was 8, blood sugar 130, chlorides 610, total protein 4.9 mgm. per cent. The CO_2 was 52.5 volumes per cent. The Wassermann reaction was negative. On x-ray examination the small intestines showed distinct puddling of the barium. There was moderate distension,



FIG. 1 THE "DEFICIENCY PATTERN" AS SEEN IN SPRUE SYNDROMES CONSISTING OF MARKED DILATATION, SEGMENTATION AND FLOCCULATION OF THE BARIUM IN THE SMALL INTESTINE

as seen in the sprue syndrome, especially of the jejunum. There was evidence of possible pressure defect in the third portion of the duodenum without distortion of the mucosal pattern. The same was true in the mid-jejunum. Dr. Sussman felt there was no evidence for inflammatory disease. It was thought that if sprue were not suggested clinically, radiologic findings were consistent with diagnosis of abdominal lymphosarcoma (Fig. 1).

A week after admission an exploratory laparotomy was done. No abnormality was found, except for numerous large soft lymph nodes, some of them measuring as much as 3 cm. in diameter. The post-operative course was fairly uneventful and the patient was soon transferred to the medical service, where his symptoms of nausea, anorexia and vomiting continued. A barium enema done at this time, about 1 month later, showed that there was general dilatation of the large intestine, and that a lymphocytosis of 70% with 10,000 white cells was still present. A note by the hematologist stated that such a finding was quite common in anorexia nervosa. The bone marrow also studied at this time was normal.

Attempts at psychiatric investigation revealed him to be a highly intelligent boy with no outward aggressions, who lately had not had his customary affection at home. He continued to have occasional periods of abdominal distention and tenderness. A scout film made at this time showed dilated loops of large and small bowel with fluid levels. An oral Janney test revealed a flat curve with a fasting sugar of 60, 100 at the half hour, 90 at the end of the first hour, and 100 at the second and third hour. The basal metabolic rate was minus 29 and the sedimentation rate 2 hours plus. In an attempt to do another Rehfuess test meal, he was found to have a gastric retention of 500 cc. His urine concentrated well at 1024.

A week after his admission a vitamin A tolerance test was done which revealed markedly impaired resorption. He had a fasting level of 51 gamma per 100 cc. of serum (normal 80-90), and a fasting level of carotene 18.6 (normal 80-150). He continued to eat very poorly all this time and continued to manifest now a diarrhea averaging 6 times per day of loose watery stools. His total protein remained low (5.1) and so he was transfused with whole blood and infused with continuous glucose and saline solution. His hemoglobin continued to remain very high, probably secondary to hemoconcentration; his stools were yellow-gray, loose and guaiac negative. He did not gain any weight.

Seven weeks after admission he was discharged with a diagnosis of diarrhea and vomiting, etiology unknown, mesenteric lymphadenopathy, etiology unknown, and, possible, anorexia nervosa. Shortly following his discharge, diastase values were found to be normal. On the theory that he had some condition that would respond to x-ray therapy, possibly mesenteric lymphadenopathy, the patient received, on the outside, 6 treatments to the anterior upper abdomen, for a total of 525 r. The factors were as follows: 190 k.u., $\frac{1}{2}$ cu. plus 1 A1, T.S.D. 40 cm., 75 r every second day between January 12th and January 24th, 1944.

He was next seen in April of 1944. He apparently was not well enough to go to school for he was studying at home. He now had 2 loose bowel movements per day and had gained 5 pounds since his discharge. He failed to report for his other follow-up appointments and was not heard from until July of 1944 when he was admitted here in an alarming condition. In the interval, that is, for the past four months, he had vomited his food occasionally, about once every few weeks, and had had bulky gray stools, but otherwise he was in fairly good condition. Two days before his admission, he complained of malaise and headache, and his temperature was found to be 101°. He suddenly began to vomit, was given 4 sulfa tablets.

following which he vomited a large amount of black fluid. He vomited several times more, only once copiously. He had 1-2 bowel movements, said to be "non-bloody and non-tarry." He was also said to have passed dark red urine 1 day before admission.

He was admitted comatose, delirious, disoriented, and bleeding from his mouth. His temperature was 98, pulse 130, blood pressure 104/60. There was only slight icterus. A large ecchymosis of left frontal bone and upper rib, and some purpura of the skin were present. He manifested convulsive jerking of the entire body. The pupils were dilated and reacted sluggishly to light. His eyeballs rolled from side to side and he exhibited bilateral masseter spasm and champing movements. Occasionally he vomited bloody material. The Trousseau test was positive but the Chvostek was negative. By rectal examination he was found to have grossly bloody stool. There was a generalized spasticity of all extremities, deep hyperreflexia, and a positive Babinski. The cremasterics were present.

The admitting impression was that this was a case of sprue with secondary acidosis, hypoprothrombinemia, and hypocalcemic tetany. The diagnoses of abdominal lymphosarcoma and Whipples' disease were also entertained. His laboratory examinations revealed a blood urea N of 20, sugar of 160, CO₂ combining power 22, cephalin flocculation 4 plus, total protein 3.9, albumin 2.6 and globulin 1.3, a calcium of 5.5, phosphorus of 3, and icteric index of 26. The clotting time was 15 minutes and bleeding time more than 20 minutes. The prothrombin index was less than 3% of normal. The stool had a pH of 6, was grossly bloody, contained abundant fatty acid crystals and moderate numbers of neutral fat globules with Sudan 3 stain. The urine was loaded with red blood cells. The hemoglobin was 78%. The red cells were 4,000,000 and the white blood cells 10,500 with a normal differential. His temperature continued to rise precipitously.

He was given calcium, vitamin K, saline and glucose and whole blood. Ten minutes after sulfadiazine was added to an infusion he went into a generalized convulsion. His condition continued to deteriorate and on the second day he died, approximately 11 months after his original complaints.

Autopsy was performed 2 $\frac{1}{4}$ hours after death. Intestinal sections were taken through the unopened as well as opened gut, in order to minimize any injury that might occur during ordinary handling. All tissues were immediately fixed in 20% formalin. In addition, mesenteric lymph nodes, carotid body, parathyroids, abdominal sympathetic ganglia, skin, pancreas, and various portions of the ileum and jejunum were fixed in 95% alcohol. Vertebral bone was fixed in Zenker-acetic acid fluid. Aside from the usual hematoxylin and eosin preparations, the liver and intestines were studied with Masson's trichrome and Ziehl-Nielsen stains. In addition, small intestinal sections were stained for alkaline phosphatase by the Gomori method and for amyloid with congo red, crystal violet, iodine green, and Lugol's stains. Sections were likewise studied with Gram's stain, as well as in silver-impregnated preparations. Toxicologic studies on the liver for arsenic, antimony, and mercury were likewise done. Frozen sections of the heart, liver, kidney and intestines were made and Sudan 3 and Smith-Dietrich stains carried out.

Tissues were prepared for the study of the distribution and quantity of alkaline phosphatase in the hope that one could visualize some changes, since disturbances in the phosphorylation (24) of carbohydrates and fats could reasonably be expected to occur. Unfortunately, there is not yet enough control material at the present time to evaluate this properly, but it is urged that enzyme studies, particularly of phosphatase, and now lipase, be carried out, especially in those cases where routine anatomical examination reveals but little. The possibility of doing this satisfactorily is strengthened by the fact that there is reason to believe that phosphatase at least, remains stable in the tissues for several days. In a similar way, the cells of the renal tubuli contorti should be studied because of the importance of this enzyme in the reabsorption of sugar at this site, and as a check on the phosphorylation process elsewhere in the body. It might be valuable also to study the phospholipids. Here, however, a much larger control material will be necessary before really significant changes can be demonstrated if present.

Postmortem Examination

The body was that of a poorly nourished normally developed 15 year old white male, in moderate rigor with moderate lividity. A peculiar sweet, mousy odor emanated from the body and pervaded the room. The skin was a brownish-tan most prominent over the thorax and there was a fairly recent hematoma present subcutaneously on the left lids and corresponding zygomatic region. The nostrils and mouth were filled with coffee-ground regurgitant fluid. There was focal hematoma formation of the upper lip. The gums were not remarkable, the teeth in moderately good condition. There was no papillary atrophy of the tongue. A 16 cm. old midline abdominal surgical scar was present beneath which wire sutures were found. In the right lower quadrant a laterally placed diagonal 8 cm. scar of similar age pointing toward the inguinal region was likewise present. Each foot was inverted and ventrally flexed, resembling pes cavus.

Abdomen: The panniculus was brownish-yellow and thin. There was recent hemorrhage into the recti muscles. There were firm fibrous adhesions to the abdominal wounds. Serosally, in the region of the cecum, and the appendiceal mesocolon, there was rather severe recent hemorrhagic effusion. This was likewise true generally in the serosal and retroperitoneal tissues. The anterior bladder wall connective tissue was likewise severely involved. The stomach was markedly enlarged. The small intestine was uniformly dilated to a moderate degree, and was more transparent than usual since its dark liquid content was visible. The transverse colon was also dilated, and bulging. This was, however, not transparent. A small scar was present at the mesenteric root. The lymph nodes were moderately enlarged, soft, and on section showed grayish-pink smooth surfaces. The nodes adjacent to the cecum showed capsular hemorrhage. The right diaphragmatic dome was at the fifth interspace, as was the left. The spleen lay above the left costal margin, the liver 1 fingerbreadth below the right in the midclavicular line.

Thorax: The pleural cavities were both dry and free of adhesions. There were no bony abnormalities. There was some air in the mediastinal connective tissue.

Heart: The pericardial sac contained about 40 cc. of clear yellow tinged fluid. The pericardium was shining and smooth. The heart weighed 175 grams, and was of flabby consistency. The foramen ovale was closed, the right auricular wall and tricuspid ring were yellow-tinged, the former showing in addition a small round purpuric area. The sinus venosus was normal. The tricuspid and pulmonic valves were delicate, and translucent. There were neither dilation nor hypertrophy of either chamber. The left as well as the right auricular appendages were normal. The mitral ring seemed somewhat dilated, but the valve, as was also true with the aortic valve, presented no abnormalities. There were multiple subendocardial round petechiae in the outflow tract. The coronary vessels had their normal site, and were free of gross lesions. The aorta was narrow, elastic and devoid of athermatous plaques. The large vessels coming off showed no abnormalities, as was likewise true of periaortic lymph nodes.

Lungs: The lungs held their shape well. They weighed 560 grams. Their pleural surfaces were smooth and shining. The underlying parenchyma was pale and showed minimal anthracotic streaking. They were moderately crepitant throughout. No subpleural nodules or apical scars were present. Section revealed an architecture that was normal except for 25-cent size scattered areas of very severe congestion. Slight pressure generally caused moderate pink frothy fluid to exude. There was no sign of aspiration, or other pneumonitis. The hilar nodes were small, anthracotic, and did not show a focus of calcification. The pulmonary vessels were thin walled, and showed no lesions. The trachea contained a small amount of frothy brownish fluid, as did the large bronchi to a lesser extent. There was hemorrhagic effusion of the superior surface of the right vocal cords. The paratracheal nodes revealed nothing remarkable.

Thyroid: This was brownish red, of normal size, showed a uniform cut surface. The parathyroids were in their usual situation, and showed no abnormalities in size, shape and color.

Liver: There was hemorrhagic effusion between the superior surface of the liver and the diaphragm. The liver weighed 1100 grams. When placed flat on the table, it was unable to maintain its shape. The capsule was transparent. Section revealed a pattern in which yellow periportal areas formed a slightly elevated rim above dark red intervening central areas. The parenchyma was unusually flabby, and moderately friable. Not the slightest resistance was offered to the knife. There was no dilation of the portal radicles, whose intima was slightly thickened. The gall bladder contained viscid dark green bile and appeared altogether normal. The biliary vessels and ducts showed no abnormalities. The liver bile was of the usual color, but slightly more viscid.

Pancreas: The pancreas bore a normal anatomic relationship to the duodenum, the duct being properly patent and emptying into the papilla of Vater. It was of the usual consistency and showed on section the characteristic pinkish-tan lobulation in which no fibrosis was grossly visible.

Spleen: The spleen weighed 210 grams. The capsule was free of abnormalities. Section showed a dark red congested pulp in which normal-appearing follicles could

be seen. The tissue scraped exceedingly well, yet was entirely coherent. The splenic vessels were normal.

Adrenals: Both adrenals were normally situated, and had an intact blood supply. Section showed well preserved gray medullae, and rich yellow cortical lipid distribution. The periadrenal connective tissue was thoroughly hemorrhagic, but the hemorrhage did not extend to the adrenal tissue itself.

G.U. Tract: The perirenal fat on the left was very sparse, and of the usual appearance. The perirenal tissue on the right was the site of severe diffuse recent hemorrhage. The left kidney weighed 160 grams, the right 200 grams. On section of the left, it was seen that the surface was grayish-pink and smooth; that the normal cortico-medullary demarcation was very indistinct; that the parenchyma was generally pale, and that a slight degree of mucosal hemorrhage was present at the ureteropelvic junction. The right presented a similar picture except for the degree. Mucosal hemorrhage of the entire pelvis with subsequent widening of the ureteropelvic junction due to clot was severe. Both ureters, and testes were without abnormalities, as was the bladder except for its surface, previously described. Prostate and seminal vesicles were unremarkable.

G.I. Tract: The entire intestinal tract contained "coffee-ground" type of blood. In the rectum alone the blood covering the mucosa was dark red in color. Except for hemorrhagic effusion into the periesophageal tissues at the level of the hiatus, the esophagus showed no lesions. The mucosa of the stomach, as elsewhere throughout the entire small intestine, seemed slightly smooth and discolored brown by the bloody content. The valvulae conniventes were more prominent, and appeared somewhat edematous proximally. Focally, but extensively, in the small intestine, one could make out certain areas with the magnifying lens which were more velvety than others. The muscle coat appeared somewhat thinned. No pigmentation was seen anywhere in the wall. The large intestine presented no apparent change in its mucosal pattern. There were two very questionable minute areas of erosion in the descending colon. The appendix was present, and showed no abnormalities.

Bone: The vertebral marrow was moist, well trabeculated, and red. There was no evidence anywhere of gross periosteal hemorrhage.

Pituitary and Brain: Examination of the pituitary and brain, confirmed and amplified by Dr. Joseph Globus, revealed no abnormalities, either on the surface or on section which showed, however, moderate vascular congestion.

Microscopic examination

Only the pertinent positive findings are mentioned:

Heart: Sections taken included representative areas from all parts of the heart. The muscle fibres were generally delicate, and for the most part were somewhat separated. There was a general but very mild stromal infiltration, consisting mainly of lymphocytes with occasional polymorphonuclear leucocytes. The outflow tract of the left ventricle showed in addition small subendocardial hemorrhages. The vessels were not remarkable. The aorta was normal.

Diaphragm: The diaphragmatic muscle showed focal areas where there was loss of normal striation.

Lungs: There was generalized hyperemia, and evidence of some lipoid aspirated material in the alveolar lumina, without tissue reaction. No changes in the bronchial epithelium were noted.

Liver: Sections from all parts revealed an essentially similar picture (Fig. 2). There was an extensive and severe parenchymal degeneration, in which the dissociation of the liver cells was striking. The individual cells, the majority of whose

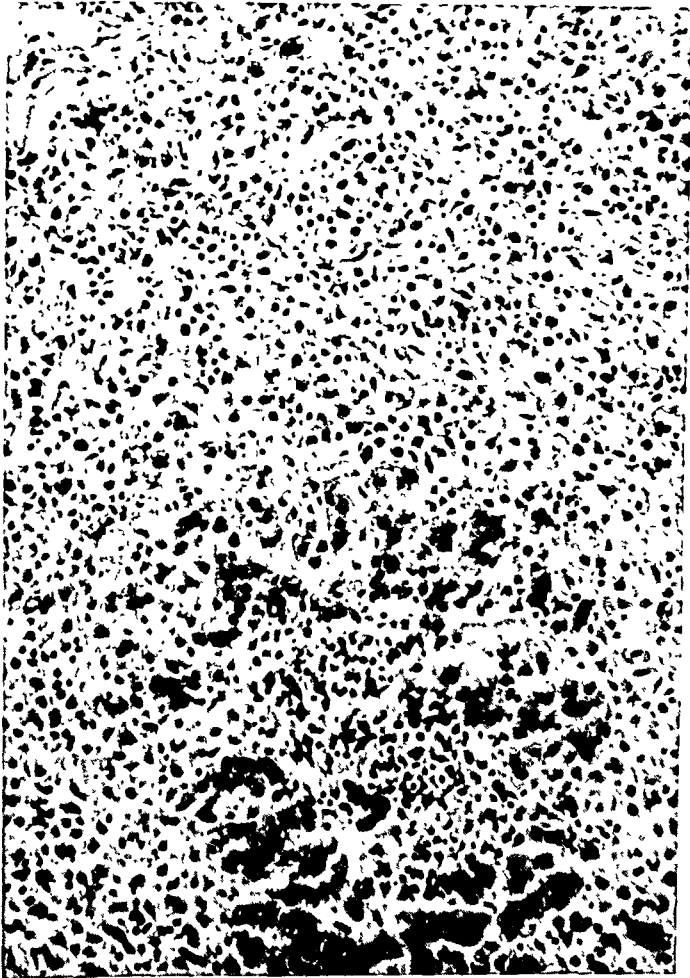


FIG. 2. SECTION OF LIVER SHOWING CELLULAR NECROSIS, AND SEVERE DISORGANIZATION OF THE ARCHITECTURE. LYMPHOCYTIC AND PLASMA CELL INFILTRATION LARGELY.
HEMATOXYLIN AND EOSIN

nuclei were maintained, varied in shape and tinctorial qualities, being, however, generally small and spindle-shaped. Many vacuoles, representing fat droplets, were present. This was confirmed with Sudan III stain. At the periphery of the lobules, in the periportal areas, there were relatively normal appearing cells. The cords were, however, very small, and the individual cells larger than usual. In this group, mitotic figures were very frequent. Here, too, fat in moderate quantities

was present. Not infrequently, there were foci of such destruction that the hepatic cells could no longer be recognized, only the framework of reticulum fibres being visible. In these areas, the remaining spindle-cells were interpreted as Kupfer cells. A striking infiltration with small round cells and relatively infrequent polymorphonuclear leucocytes was noted. Connective tissue proliferation was not seen, with special stains or otherwise. No ceroid was noted anywhere.

The portal spaces were filled with inflammatory cells, composed almost exclusively of lymphocytes, only occasional plasma cells, and polymorphonuclears being seen. The portal vessels and bile ducts were not remarkable.

Toxicologic studies for the heavy metals were negative.

The *gallbladder*, *thyroid*, *prostate*, *tongue*, *carotid body*, and sections from splanchnic ganglia were essentially normal. The *parathyroids* were markedly congested and hemorrhagic. This was likewise true of the *periadrenal* tissues, and to a slight extent in the cortices of the glands, which were otherwise not remarkable. Sections from voluntary *muscle* almost everywhere showed similar hemorrhagic effusion. Similar changes were present in almost all the investing *connective tissues*. No changes were noted in the *bladder* epithelium. The testes showed normal spermatogenic activity. Aside from marked congestion, the presence of a somewhat increased number of polymorphonuclear leucocytes and lymphocytes, and of many of those large cells with densely staining basophilic cytoplasm and nuclei, known as "splenocytes", the *spleen* was not remarkable. No unusual numbers of Russell's bodies, as has been elsewhere reported, were noted. Except for focal medullary congestion and hemorrhage, slight degenerative changes in the tubular epithelium, and the presence of a slightly basophilic precipitate in Bowman's capsule and the collecting tubules, the *kidneys* were anatomically normal. No changes were noted in the pelvic epithelium. They were not stained for phosphatase activity. The *pancreas* which was well preserved showed slight acinar atrophy, with moderate paucity of the zymogen granules. The islets of Langerhans were large, and numerous as seen in hunger-states. Other abnormalities were not noted. There was very marked alkaline phosphatase activity of all the capillary walls, and some activity in the nuclei of the acinar and islet cells. Except for definite, though mild, infiltration of the stroma with small round cells preponderantly, the *salivary glands* were normal.

Sections of abdominal *skin* showed no abnormalities except for a considerable increase in the melanin-bearing chromatophores of the basal layer of the epidermis.

The examination of the *pituitary* and *brain*, confirmed and amplified by Dr. Joseph Globus, was as follows:

Pituitary: No abnormalities noted; *Brain*: paraffin section of cortex and sub-cortex showed only meningeal vascular engorgement; celloidin preparations from the right temporal lobe revealed "an obvious increase of glial nuclei. In some areas the nerve cells appeared in various stages of degeneration. The cell bodies were shrunken and nuclei pyknotic. . . Diagnosis: "primarily a degenerative encephalopathy". Nissl preparation supplied no further information. The inguinal, cervical, and lumbar as well as mesenteric *lymph nodes* were examined. The first group

showed an essentially similar picture, and consisted of essentially normal nodes. The *mesenteric* nodes (at autopsy) were without significant change.

Re-examination of the *mesenteric lymph node biopsy* done approximately nine months before death showed the capsule and adjacent fat tissue to be infiltrated by lymphocytes, and occasional plasma cells. The lymphatic tissue was dense, and the cortical follicles large. The septa revealed a moderate number of plasma cells, and occasional polymorphonuclear leucocytes. The sinuses showed a proliferation of the reticulum and endothelial cells.

Intestinal tract: Sections from various portions of the esophagus and stomach were studied, and, except for slight mucosal atrophy of the pyloric portion where a mild infiltration consisting predominantly of small round cells, of the mucosa and submucosa was likewise present, they were found normal.

Multiple sections were studied from every portion of the *small intestine*, and each revealed qualitatively similar changes. Only the severity of the microscopic lesion varied, and this in a completely irregular manner. Although there was no, or minimal at the most, atrophy of the submucosa or the muscular tunics, the mucosa was definitely atrophic. All sections revealed only very slight autolytic changes, which did not obscure in any way the lesions to which attention is called. The most striking changes were in the over-all conformation of the villi which had lost their characteristic elongated rather slender papillary form, and had now become broad based, squat, bulbous, and plump (Fig. 3A). When compared with the finger-like projections of the normal small intestine as seen at autopsy (Fig. 3B), the alterations became even more distinct. This villus clubbing produced an impression of rigidity of these structures. Occasionally, another type of deformity was noted, in which a relatively slender villus stalk was surmounted by an umbrella-shaped apex. This may be most adequately described as "mushrooming" of the villus. The lesions depicted represented the more severely affected areas.

There was some post mortem desquamation of the lining epithelium. In each section, there was a deposition of hyaline material, located preponderantly at the apices of the villi just beneath the basement membrane, in the form of bands which occasionally completely, and at other times only partially, traversed the entire villus diameter. Only occasionally, most of the villus was replaced by hyaline material. The majority of these villus tip bands were continuous with the reticular network and also implicated the capillary walls (Fig. 4). In the lesions which were considered to be at an earlier stage, it could be seen that the reticulated fibrillar structure had become eosinophilic, thicker, and more rigid than normal. The capillaries, and venules were distorted, and the lacteals could be identified only with relative difficulty. This, as well as the gradual obliteration of the normal network, was conceived as resulting from the compression by this material, which, in the silver preparations, could be seen to be laid down as a mantle about axes of reticular fibres. In the lesions that had progressed further, the reticular structure disappeared, although one could still recognize remnants of argyrophile fibres in the compact hyaline bands. Comma and spindle shaped cells, some of which appeared to represent vascular endothelial cells and others fibroblasts, were occasionally seen irregu-



A



B

FIG. 3. A. Section from the proximal ileum showing the characteristic villus clubbing with hyaline band formation at the villus tips. B. Section of a normal small intestine from approximately the same region (autopsy specimen). Hematoxylin and eosin.

larly embedded in the villus tip bands. In no instance did this process extend down between the crypts. The cellular composition of the villi was not remarkable. There were good numbers of polymorphonuclear leucocytes present, predominantly neutrophilic, with moderate numbers of eosinophiles. There was no increase in the numbers of lymphocytes and plasma cells. Frozen section preparations with Sudan showed some orange-yellow staining of portions of the lesions, while similar



FIG 4 SECTION FROM THE DISTAL ILEUM SHOWING THE RELATIONSHIP OF THE HYALINE BANDS TO THE RETICULAR AND VASCULAR STRUCTURE OF THE VILLUS HEMATOXYLIN AND EOSIN

preparations, gelatin-embedded, showed only small amounts of phospholipids in these villi with the Smith-Dietrich method. Attempts were made repeatedly to identify the hyaline material as amyloid. These were invariably unsuccessful. With Masson's trichrome stain, this material took on an intense green color. Ceroid could not be identified with the Ziehl-Nielsen stain. Sections stained by Gram's method revealed relatively few numbers of Gram negative rods, as well as Gram positive rods and cocci, superficially located. The alkaline phosphatase

studies revealed prominent activity of the capillary endothelium and nuclei of the lymphocytic, histiocytic and plasma cells of the stroma. The mucosal lining showed only moderate nuclear and very slight cytoplasmic activity. Although in the present state of our knowledge, no conclusions can be drawn since these comparisons offer serious difficulties, Dr. M. Wachstein² in studying normal animal intestines found very much stronger cytoplasmic epithelial, and much less stromal, activity. However, the weak staining might be partially a postmortem effect in this case.

The submucosa was not atrophic, did not contain undue numbers of leucocytes, and showed arteries, veins and lymphatics that appeared normal in every way. The plexus of Auerbach and Meissner were well preserved, and with the ordinary histological technics showed no changes. It is felt that in certain cases of intestinal dysfunction, the application of the finer neurohistological techniques might be rewarding. There was some separation of the fibers of the muscular coats, interpreted as due to occasional foci of perivascular infiltration with small round cells. The serosa revealed nothing remarkable.

Large intestine: There was an abundant outpouring of mucus to the intestinal surface. In general, the crypts remained closely approximated, but occasionally they were spread apart. In such areas, the stroma showed increased numbers of eosinophilic leucocytes and plasma cells.

Vertebral bone marrow: For this age (15) there was an increased amount of fat. There were no changes noted in the osseous trabeculae. The distribution of all the elements was not materially altered except that the megakaryocytes were at the lower limits of frequency, one being found approximately in each high-power field. No abnormalities were found in the erythroid series which was studied especially closely.

Comment: Two hundred small intestinal sections, representing many types of autopsied case, were carefully re-examined, especial attention being paid to the villus tips and capillaries. Only those cases were chosen in which the postmortem changes were minimal. In none were similar lesions found. Because of the history of abdominal radiation, it was necessary to re-evaluate those cases which had undergone x-ray therapy over the anterior abdomen. For this purpose, 45 cases, which had received varying but always significant doses of x-rays to the anterior abdomen were culled, on the basis of minimal autolytic change, from a much larger group. These included chronic myeloid and lymphatic leukemias, follicular lymphoblastomata, lymphosarcomata carcinomata of the female genital tract, etc.

Although other classical findings such as vascular changes and ulcerations were noted, in no case were lesions observed similar to those found in the case reported above. A review of the literature (23, 29, 42, 60, 63, 65, 86, 87, 90) concerned with the effects of radiotherapy on the intestines failed to disclose a single instance of similar anatomical alterations. In this connection,

² Personal communication.

it is however of interest to note that in 1922 Mottram (59), Cramer and Drew could inhibit the absorption of fat in rats in direct proportion to the dosage of radium to the intestines. They believed that this effect resulted from a decreased leucocyte count, but Martin (54, 56), in 1924, in an effort to clarify the mechanism administered radiation to the exposed small intestinal loops of 3 dogs in doses of 15, 37.5 and 75 m.a. per minute, the smallest being chosen because it could produce a minimal visible erythema on the human skin. The factors used were a 9 inch parallel gap, a 10 inch focal skin distance, with a 2 mm. filter of aluminum. A week following this procedure they were able to demonstrate at laparotomy that the animal receiving the smallest dose possessed mesenteric lymphatics grossly distended with absorbed fat 3 hours after a cream feeding, but that in the other 2, following similar treatment, no lymphatics were visible at the site of damage. Villus tip lesions were however not present, the outstanding histologic changes being a marked increase in mucus and a lack of intracellular fat. A few small ulcerations were observed. They felt it probable that the lack of fat absorption might be accounted for by the large amount of mucus.

In view of this, the possibility of the production of a deficient fat resorption (or sprue-like syndrome) in man under similar circumstances must be entertained. The probability of a patient's receiving comparable doses is however not very great. The question of whether an intestinal mucosa which is anatomically whole but physiologically subnormal may not be unusually susceptible to otherwise harmless or small doses of x-ray cannot be answered here, but it is another factor which should be borne in mind.

Because of the realization that amyloid deposition may occur prominently at the villus tips and in the lamina propria, constituting therefore a possible mechanical barrier to absorption, 40 cases of intestinal amyloidosis, "primary" and secondary to varying causes, were chosen with regard to preservation from postmortem changes. Although many had diarrhea and melena, only two had what in retrospect could be interpreted reasonably as a sprue syndrome. In these cases, the lamina propria, as well as the villus tips, contained a great deal of amyloid material, and this may have contributed to the intestinal dysfunction. In addition, one case showed especially severe involvement of the submucosal vessels. It must however be admitted that the one other case where amyloid was especially prominent at the villus tips did not show at all the gross clinical picture of the sprue syndrome. This is not surprising in the light of the common knowledge that amyloid interferes remarkably little with the function of an organ. Nevertheless, it may theoretically tip the scale, and therefore it is one other intestinal anatomical factor to be considered in the causation of the symptom complex of sprue.

It was deemed necessary because of the liver disease present in this case

to study other instances of acute and subacute liver atrophy with special attention to the small intestinal villi. Here too cases were chosen where there was good postmortem preservation. These included only 3 satisfactory cases of the acute variety and 12 of the subacute and chronic type. In none were similar small intestinal changes found. Although it is of course realized that this is a very small amount of material, a search through the literature concerned with acute and subacute liver degenerations (31) failed to disclose such a process. The most recent careful study of a large number of fatal epidemic hepatitis, made by Lucke (47), likewise confirms the lack of similar lesions in severe hepatic damage.

Although liver disease of some type, because of the wasting illness, can be expected to be present in any instance of the sprue syndrome, the termination of this case with an acute liver necrosis is unique. There was no evidence to be found for any of the known liver toxins, nor was it thought at all likely that sulfasuxidine could be held responsible for the hepatic damage, as suggested by the work of Gross, Axelrod and Bosse (22) in subnormally nourished rats, where striking liver necroses were found in more than half the sulfaguanidine-treated animals, (it being stated that similar lesions could be produced by the sulfasuxidine). It was thought far more probable that the patient was primarily a liver invalid, secondarily to malabsorption of essential foods, who succumbed therefore relatively easily to unknown noxious agents. However, it is believed that since there could be found no anatomical substratum for chronic liver disease, we have no solid ground for considering that the liver had any bearing on the sprue syndrome in this case. There was no hint of other hepatotoxins, not even arsenic in the form of the much used Fowler's solution. Since this type of patient receives sulfasuxidine often, it will be interesting to see in the future whether cases of sprue come to autopsy with more striking liver complications than those noted in the past.

There was no evidence anywhere to suggest that drugs the patient might have obtained could produce such intestinal lesions.

The role and the significance of the mesenteric lymphadenopathy is a difficult one to ascertain. To speculate on the constitutional significance of the persistent lymphocytosis and mesenteric adenopathy in this 15 year old boy would be without profit. The fortunate circumstances of having a mesenteric lymph node biopsy in the fourth month of the disease which revealed a definite though mild inflammatory change lends support to the idea that an active enteritis was present during this time. Against the point of view that a secondary low-grade enteritis occurred in an already functionally injured bowel is the rather clear cut clinical onset of the sprue syndrome shortly after an episode of diarrhea and general malaise, reminiscent of a "grippe."

Because of the possibility that poor nutrition might in some way produce

the unusual lesions described, it was decided to search in the literature along these lines, since our own material in such cases where chronic hunger could reasonably be expected to be present was not satisfactory from various viewpoints, especially from those of postmortem changes, and the universal use of parenteral feeding. It is of interest to note that, although no similar small intestinal changes aside from atrophy could be found, Siegmund (67) reported that cases of "Hungeratrophie" showed a "mucous colitis" associated with increased numbers of leucocytes in the framework of the glands. It could be said that similar findings existed in this case.

SUMMARY

1. A critical review of the pathologic changes of the small intestine in sprue, as reported in the literature, is made.

2. A case of sprue syndrome with unusual termination (liver necrosis) and previously undescribed histologic lesions of the small intestine is reported. The latter consist principally of an unidentifiable hyaline material disposed mainly as villus tip bands over the upper portions of villi whose characteristic deformation is "clubbing" and "mushrooming."

3. The possible role of other etiologic factors and associations with the sprue syndrome (x-ray therapy and amyloid disease) is discussed.

4. The future study of the intestinal pathology of this symptom-complex should take into account a meticulous autopsy technique, as well as proper fixation for enzymes concerned with the transport of food stuffs across enteric membrane. It is believed that search in other cases of the idiopathic sprue may be rewarded by similar findings.

Addendum: Several months after the above study was completed, a 71 year old man, who had suffered from a disease characterized by diarrhea, came to necropsy. His clinical picture generally was such that a diagnosis of a sprue syndrome could be made. In so far as the latter component of his illness was concerned, the pathologic findings in the small intestine were of interest. Microscopic examination disclosed here also, though to lesser extent, villus clubbing, and hyaline villus tip bands.

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ORAL CHOLECYSTOGRAPHY WITH PRIODAX

CORRELATION WITH PATHOLOGIC FINDINGS

J. L. JARVIS, M.D., AND DAVID CAYER, M.D.

From the Department of Radiology, North Carolina Baptist Hospital and Department of Internal Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.

INTRODUCTION

The development of radio-opaque substances which are excreted in the bile when given orally or intravenously has been one of the greatest forward steps in the accurate diagnosis of gallbladder disease. In recent years much experimental and clinical work has been done to develop dyes of greater radio-opacity and increased safety. In 1940, Dohrn and Diedrich reported results with cholecystography using beta (4-hydroxy-3,5 diiodophenyl) A-phenyl-propionic acid (Priodax) and emphasized the reliability and low toxicity of this substance (1). Their report has since been substantiated in many clinical studies (2).

When x-ray findings can be evaluated by operative follow-up and pathologic study, the accuracy of x-ray studies, as well as the possible sources of error, can be determined. In the following study this method was used to determine the diagnostic accuracy of cholecystography in the North Carolina Baptist Hospital.

MATERIAL

Eighty consecutive cases were studied in which the preoperative diagnosis of cholecystitis with or without stones was made. They were divided on the basis of the roentgenologic reports as follows: *Group I*, normal visualization; *Group II*, faint visualization; *Group III*, no visualization. Each group was further subdivided into: *a*, Stones present; *b*, Stones probably present; *c*, No stones. The number of patients in each group is seen in Table I.

The roentgenologic report was then compared with the findings at the time of laparotomy and with the reports received from the Department of Pathology, based on the gross and microscopic findings.

METHOD

Preceding cholecystography, the following regimen was adhered to: (1) The patient was given a breakfast and lunch rich in fats. (2) No fats were allowed with the evening meal. (3) During or immediately after the evening meal, the patients were given 10 Priodax tablets, each containing 0.5 grams of the dye. (4) No fatty foods were allowed after the dye was taken, but the patients were allowed to have sweetened fruit juices during the evening. (5) The patients

were given a soap suds enema before 7 o'clock on the morning of examination. (6) Breakfast was omitted, although 3 ounces of fruit juice were allowed.

X-ray examination was made at 8:30 a.m. (fifteen hours after administration of the dye). Two techniques were used. For the first year an 8 x 10" film was used in a cassette with cone, the patient being in the posterior-anterior position. For about the past year and a half 8 x 10" and 10 x 12" films have been used in a cassette with cone, the patient being in the posterior-anterior position.

TABLE I
Roentgenologic Reports

GROUP	VISUALIZATION	STONES	PROBABLE STONES	NO STONES
I	Normal (15)	10	1	4
II	Faint (32)	19	8	5
III	None (33)	5	3	25

TABLE II
Group I—Normal Visualization

SUBGROUP	NO. OF PATIENTS	X-RAY REPORT—STONES	OPERATION—STONES PRESENT	PATHOLOGIC REPORT
a	10	Positive	9	Cholesterosis (without stones)..... 1 Chronic cholecystitis (with stones)..... 9
b	1	Probable	1	Chronic cholecystitis (with stones)..... 1
c	4	None	0	Normal..... 1 Cholesterosis..... 1 Chronic cholecystitis (without stones)..... 2

RESULTS

Group I: normal visualization (table II). The gallbladder was reported as well visualized in 15 patients. In 9 of the 10 patients in this group diagnosed by x-ray as having cholelithiasis, stones were found at operation; the pathologic report in each instance was chronic cholecystitis. The remaining gallbladder specimen showed cholesterosis.

In the 1 case reported as showing "probable stones," calculi were present at the time of operation. None of the 4 patients whose gallbladders were reported as "normal" were found to have calculi at operation. Pathologic examination revealed chronic cholecystitis in two instances, and cholesterosis in one. The remaining specimen was reported as normal.

Group II: faint visualization (table III). There were 32 patients in whom

both concentration of the dye and contraction of the gallbladder after the fatty meal indicated impaired function. In 19 of these cases the definite x-ray diagnosis of cholelithiasis was made, and in each instance calculi were found at

TABLE III
Group II—Faint Visualization

SUBGROUP	NO. OF PATIENTS	X-RAY REPORT—STONES	OPERATION—STONES PRESENT	PATHOLOGIC REPORT
a	19	Positive	19	Normal (with stones)..... 1 Cholesterosis (with stones)..... 2 Chronic cholecystitis (with stones)..... 16
b	8	Probable	6	Cholesterosis (without stones)..... 1 Chronic cholecystitis (without stones)..... 1 (with stones)..... 6
c	5	None	3	Chronic cholecystitis (without stones)..... 1 Cholesterosis (without stones)..... 1 Chronic suppurative cholecystitis (with stones). 1 Chronic cholecystitis (with stones)..... 1 Gangrenous (with stones)..... 1

TABLE IV
Group III—No Visualization

SUBGROUP	NO. OF PATIENTS	X-RAY REPORT—STONES	OPERATION—STONES PRESENT	PATHOLOGIC REPORT
a	5	Positive	5	Chronic cholecystitis (with stones)..... 5
b	3	Probable	3	Chronic cholecystitis (with stones)..... 3
c	25	None	22	Adeno-carcinoma of the gallbladder (with stones) 1 Metastatic carcinoma (without stones)..... 1 Acute and chronic cholecystitis (with stones)..... 1 (without stones)..... 1 Gangrenous (with stones)..... 1 Cholesterosis (with stones)..... 1 Cholesterosis (without stones)..... 1 Chronic cholecystitis (with stones)..... 18

operation. Pathologic study revealed cholesterosis in 2 gallbladder specimens, 16 gallbladder specimens showed evidence of chronic cholecystitis and one was reported as normal.

In 8 instances stones were reported as probably present on x-ray examination.

Six of these patients were found to have stones at the time of operation. Pathologic examination showed 1 instance of cholesterosis and 7 of chronic cholecystitis.

In 5 of the cholecystograms showing impaired concentration or function, no stones could be seen. At operation 3 of these patients were found to have cholelithiasis. Pathologic study in this group revealed evidence of old and recent infection. Three gallbladder specimens were reported as showing chronic cholecystitis; one was a gangrenous gallbladder with stones, and the remaining specimen showed cholesterosis.

Group III: no visualization (table IV). There were 33 patients in whom the cholecystogram showed no concentration of dye. In 25 of this group no stones could be visualized. At operation, however, 22 of these patients, or 88 per cent, were found to have calculi present. In no instance was a normal gallbladder found. Pathologic reports are given in table IV. In each of 5 instances where calculi were demonstrated by x-ray, they were found at operation. The pathologic examination in each case showed evidence of chronic disease. The 3 patients in whom calculi were reported as probably present were all found to have stones.

DISCUSSION

The most important single development in the study of function and disease of the gallbladder has been cholecystography. The use of other accessory clinical studies as aids in the diagnosis of gallbladder disease has become increasingly important with the standardization of procedures and improvement of technique. The case history remains a most important factor in diagnosis, particularly in the diagnosis of acute gallstone attacks. Chronic cholecystitis is not nearly so simple a diagnostic problem, and dyspeptic symptoms occurring in middle-aged persons showing decreased function or stones by cholecystogram are more difficult to interpret.

A study of the tables reveals that, in general, the accuracy with which cholelithiasis can be diagnosed varies directly with the ability of the gallbladder to function.

Group I: normal visualization. Where function was reported to be good, calculi were found in 10 of 11 cases in which they were reported as present or probably present by cholecystogram. The remaining patient had an episode of colic just before operation, and it was felt that a calculus might have been passed at the time. In the 4 patients from this group in whom no stones were seen by x-ray, none were demonstrated following operation.

The presence of stones in a gallbladder with good function, as judged by its ability to concentrate and contract and provide "normal visualization," suggests that functional recovery may follow an inflammatory process or metabolic

disturbance. It is reasonable to assume that recovery might occur following such a disturbance without the formation of stones. In 3 out of 4 patients whose gallbladders were reported to show normal function and no stones, definite pathologic changes were demonstrated by gross and microscopic study. These 3 patients have been symptom-free since operation (eighteen to twenty-six months). The fourth patient, who has also been asymptomatic, had a carcinoid tumor of the appendix removed at the time of cholecystectomy.

It is in this group of patients with symptoms suggestive of chronic cholecystitis, but in whom the cholecystogram shows good function without stones, that clinical evaluation is most difficult. Final diagnosis in such instances must depend upon the clinical history and careful accessory studies, including repeated examination of the bile obtained by duodenal drainage, particularly for the presence of cholesterol crystals and calcium bilirubinate pigment (3). The demonstration of good concentration and function by cholecystography, associated with repeatedly normal findings by biliary drainage, makes the diagnosis of chronic cholecystitis and cholelithiasis unlikely. Ravdin has emphasized the poor results which follow cholecystectomy in the absence of stones, even in cases where low grade cholecystitis is demonstrated pathologically.

Group II: faint visualization. Where the cholecystogram showed impaired function, the positive diagnosis of cholelithiasis was made in 19 patients and confirmed in each instance at operation. With a single exception, all the gallbladders showed pathologic changes consistent with cholecystitis and cholelithiasis. Stones were demonstrated in 6 of 8 instances where they were reported as probably present on x-ray examination. It is of interest that calculi were found at operation in 3 of 5 patients who had impaired function, but in whom no stones were visualized. This error is even more striking in group 3.

Group III: no visualization. Whereas the roentgen diagnosis of cholelithiasis was most accurate in cases where good or fair gallbladder function was found, and the diagnosis of cholecystitis, when compared with the pathologic reports, was least accurate in these cases, the reverse was true in the patients whose gallbladder function was markedly impaired and who showed little or no concentration of the dye or contraction of the gallbladder following the fatty meal. Marked pathologic changes were found in each such case. Where stones were reported as definitely or probably present, in every instance their presence was confirmed at operation. Though no stones were visualized in 25 cases, they were found in 22, or 88 per cent of these, at operation. Thus, a large percentage of patients whose gallbladders show little or no ability to concentrate the dye or to contract will be found to have stones at operation, although the cholecystogram may fail to reveal their presence. In the absence of technical errors, disorders of absorption, jaundice, liver disease, or an obstructed cystic duct, failure to visualize the gallbladder shadow after repeated

examination is a most reliable indication of gallbladder disease and is presumptive evidence of cholelithiasis.

SUMMARY

In 80 consecutive patients who came to cholecystectomy, the operative and pathologic findings were compared with the preoperative x-ray interpretation following oral cholecystography with Priodax. The x-ray diagnosis of cholelithiasis was most accurate and the diagnosis of cholecystitis was least accurate where the ability of the gallbladder to concentrate and contract was least impaired. Repeated failure to demonstrate a gallbladder shadow after administration of the dye is a highly reliable indication of disease, and is presumptive evidence of stones. At operation, 88 per cent of such patients were found to have non opaque calculi which had not been visualized by previous x-ray examinations.

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A PRELIMINARY REPORT ON PROTEIN HYDROLYSATE THERAPY FOR PEPTIC ULCER

SERUCH T. KIMBLE, JR., M.D.

Bethesda Suburban Hospital, Bethesda, Maryland

INTRODUCTION

Since Co Tui's report in July, 1945 (3), on the value of protein hydrolysate in treating peptic ulcer, considerable interest has been focused on this subject. His series included 30 patients who were put on feedings of dextrimaltose and protein hydrolysate at two-hour intervals. The mixture yielded from 0.5 to 0.8 gm. of nitrogen and from 40 to 50 calories per kilogram of body weight per day. All of the patients experienced relief of distress within 24 hours and subsequent roentgenograms revealed rapid improvement in the ulcers. The number of cases was small and the follow-up studies incomplete, but the results were so suggestive that this therapeutic technique certainly merits further study (5).

The following is a preliminary report on 13 cases of duodenal ulcer, 1 of combined duodenal and gastric ulcer, and 1 of gastric ulcer alone, treated with a 6 per cent solution of protein hydrolysate administered by gastric drip and venoclysis. The study was performed in a 100-bed private hospital with few research facilities. Fourteen of the fifteen patients were private cases, which also tended to limit the uniformity of the study. Clinical and roentgenological results were so striking, however, that it is felt they are worthy of communication.

METHOD OF STUDY

The Product. The protein hydrolysate which was employed has the composition shown in Table I.

This protein hydrolysate is a heat-sterilized, stable, pyrogen-free, enzymatic derivative of beef. It contains no undigested proteins or proteoses, and a liter of the 6 per cent solution is equal to 60 gm. of protein. Approximately 50 per cent of the nitrogen is free amino nitrogen and 1 per cent is ammonia nitrogen. The pH is 6.5, and 100 cc. of solution will neutralize 50 cc. of 0.1 normal HCl. No deterioration occurs when the clear amber liquid is kept at room temperature.

Administration. The method of administering protein hydrolysate varied from patient to patient; improvements were made as the number of cases increased and modifications employed to fit the particular situation at hand. No specific therapy was instituted without X-ray proof of the presence of an ulcer.

In 11 cases a Levine tube (size 14-16) was inserted into the cardiac portion of the stomach. Through this tube, which remained in place for 7 days, a continuous drip of protein hydrolysate, alternated with equal parts of whole milk and 20 per cent cream, was administered. Five-hundred cc. of hydrolysate at the rate of 25 drops per minute was alternated with 600 cc. of milk and cream at 50 drops per minute. During each 24 hours the patient received 1500 cc. of hydrolysate (90 gms. of protein) and 1800 cc. of milk and cream.

Five individuals were treated with continuous gastric drip for 7 days and

TABLE I
Composition of Protein Hydrolysate

COMPONENT	PER CENT
Amino acids } Polypeptides }	6.0
Nitrogen.....	.625
alpha amino.....	.325-.390
ammonia.....	.004-.008
Ash.....	.85
Water.....	93.15

TABLE II
Daily Intake

COMPONENT	HYDROLYSATE ADMINISTRATION	
	GASTRIC DRIP	INTRAVENOUS
	gm.	gm.
Calories.....	2780	2000
Carbohydrate.....	90	58
Protein.....	143	126
Fat.....	216	140
Mineral Ash.....	23	20
Water.....	2830	2330

then with venoclyses of protein hydrolysate (500 cc. t.i.d.) for 2-3 days. Case XII, who was hemorrhaging profusely on admission, received 10 days of drip treatment followed by venoclyses. Four patients were given hydrolysate by the intravenous route alone, 1500 cc. being administered daily for 7-10 days. This was supplemented with 3 ounces of milk and cream hourly during the day.

Analysis of Daily Intake is shown in Table II.

According to White and Weinstein (6), 70 gm. or more of protein are required every 24 hours to maintain nitrogen balance after surgery. The patients in this study were non-surgical but received 143 gm. of protein daily by gastric drip and 126 gm. daily when hydrolysate was administered by venoclysis, sup-

plemented with oral milk and cream. Thus all patients were presumably in positive nitrogen balance, although laboratory proof was not obtained.

Supplementary Measures. A complete hemogram and urinalysis were performed on each patient. Total serum proteins and body weights were determined both before and after therapy in 11 and 12 cases respectively. The presence of an ulcer was invariably confirmed by fluoroscopic and film studies before treatment was instituted, and its status checked immediately after the course of therapy.

The proposed course of treatment was explained to each patient with emphasis upon control of the ulcer rather than cure. As recommended by Co Tui (2), the importance of personal discipline and the ability to lead a sane "peptic ulcer" life was repeatedly stressed. Patients were allowed bathroom privileges unless actively hemorrhaging. Smokers were requested not to exceed 6 cigarettes daily.

Supplementary medication varied from case to case. One-half grain of phenobarbital t.i.d. and 10 minims of tincture of belladonna t.i.d. a.c. were routinely prescribed. Each evening 3.75 grains of sodium amytal was given hypodermically to insure sound, restful sleep. Oral and parenteral vitamins were ordered in cases of hemorrhage or persistent vomiting. Because of its important role in tissue repair and in reducing the urinary excretion of aromatic amino acids, ascorbic acid (200 mgm. daily) was ordered in most cases (1). Liver, iron, and transfusion if necessary were prescribed for patients with hemorrhage. After removal of the Levine tube, the following daily regimen was adopted:

1. 3 bland meals at 8, 12, and 6.
2. 3 ounces of equal parts of whole milk and 20 per cent cream at 10, 2, and 4.
3. Phenobarbital 0.5 gr. t.i.d.
4. Tr. of belladonna minims X t.i.d. a.c.
5. Antacid at 7, 8, and 9 P.M.
6. Nothing orally after 9 P.M.

Those 4 patients who received protein hydrolysate solely by venoclysis (500 cc. t.i.d.) were put on the above routine at the end of 7-10 days. Six cases out of 11 treated by gastric drip also received hydrolysate intravenously for 2-3 days after removal of the Levine tube.

CLINICAL MATERIAL

This study includes 13 patients with duodenal ulcer, 1 with combined duodenal and gastric ulcer, and 1 with gastric ulcer alone. With the exception of cases III and XV, they possessed the physical and emotional characteristics of the ulcer type as outlined by Draper (4). They were intense individuals, curious about their surroundings and possessing an appraising glance. The

face was narrow, the chin pointed, the teeth rather long and presenting a sharp biting edge. Body lines in general were linear rather than thick. These people were physically and emotionally hyperdynamic and usually of superior intelligence. Although inclined to worry, they had a keen sense of humor and were emotionally very responsive.

The age range of the group was from 30 to 69 years, the average being 44 years. There were 2 white females, 12 white males, and 1 colored male in the series. Epigastric distress was the outstanding symptom in all cases and had been present for 4 days to 15 years before admission. Four patients developed hematemesis just prior to hospitalization but the others had no signs or history of hemorrhage. Two patients who had been ill less than a week suffered with intractable vomiting. Six cases had been previously treated unsuccessfully with bed rest and a Sippy diet, while 3 had roentgenologically demonstrable gastric retention 6 hours after administration of the barium meal. No patient had had a perforation or previous surgery on the stomach or duodenum.

TABLE III
Effect of Age and History on Recovery

X-RAY RESULTS	NUMBER OF PATIENTS	AVERAGE AGE	DURATION OF ULCER
		years	years
Complete recovery.....	9	41.5	2
Marked improvement.....	5	46.5	5

INDIVIDUAL CASES

Case I. J. M., 37 year old white male. Occupation: Auto stock clerk.

Ulcer history. For 3 years preceding hospitalization, the patient had experienced a dull epigastric pain 3 hours after meals. It was usually relieved by food, and there was no history of vomiting, hemorrhage, or signs suggesting perforation. General malaise and a dull frontal headache frequently accompanied epigastric distress. The patient had been to several doctors who had labeled him as neurotic and sent him on his way. Neither X-ray studies nor peptic ulcer therapy had been attempted.

X-ray Findings. On 11-15-45 fluoroscopic and film studies of the gastrointestinal tract with the barium meal method revealed the stomach to be normal in size, shape, and position. Peristalsis was hypertonic but no gastric filling defect was noted. The duodenal bulb showed a constant deformity with a crater formation in its medial border. A barium fleck remained in the crater after emptying of the duodenum and was still visible in the 6-hour film.

Treatment. On 11-21-45 a Levine tube was inserted into the cardiac portion of the stomach and a continuous gastric drip was started. It consisted of 1500 cc. of protein hydrolysate at the rate of 25 drops per minute, alternated with 1800 cc. of milk and cream at twice that rate. After several days, the milk and cream caused nausea and generalized gas pains. Protein hydrolysate also nauseated the patient, and he vomited once during its administration. Thereafter, 500 cc. of hydrolysate was

alternated with 600 cc. of milk and cream, the rate of flow remaining the same. All discomfort immediately subsided.

On 11-28-45 the Levine tube was removed, 7 days after its insertion. Treatment then consisted of 3 bland meals daily and the other measures previously outlined. In order to minimize nocturnal gastric secretion, nothing was allowed orally after 9 P.M.

Results. Roentgenologic reexamination on 11-30-45 revealed the barium meal to pass in normal rate and fashion. The duodenal bulb filled smoothly, had a normal contour, and emptied freely. No evidence of the previous ulcer remained. During treatment, the total serum protein rose from 4.1 to 5.5 gm. per cent, and the patient gained 3 pounds. His feeling of strength and general well-being was much improved.

Follow-up. For several weeks following hospital discharge, the patient had nocturnal epigastric distress, which was quickly relieved with antacid. Seven weeks after discharge, repeat fluoroscopic and film studies revealed no evidence of ulcer or other pathology in the stomach and duodenal bulb. Peristalsis continued to be normal and the patient had become completely free of ulcer symptoms. X-ray examination was repeated 15 weeks after discharge and showed no recurrence of gastrointestinal hyperirritability or duodenal ulcer. The patient was still symptom-free, his total serum protein had risen to 6.5 gms. per cent, and his initial weight gain of 3 pounds had been maintained.

Case X. L. P., 31 year old colored male. Occupation: Cement finisher.

Ulcer History. This patient developed his first symptoms in May, 1945. At that time he noted a "drawing" sensation in the left upper quadrant, close to the midline. It was a dull ache, rather than a pain, and frequently radiated a few inches to the left. There was no definite time relation of abdominal discomfort to eating, but it usually occurred at 4 or 5 P.M. and lasted 1 hour. The patient had not vomited, hemorrhaged, or had other complications.

Fluoroscopic and film studies on 11-9-45 revealed a constant deformity of the duodenal bulb, which could not be smoothed out during fluoroscopic palpation of the abdomen. The diagnosis of duodenal ulcer was made and the patient placed on strict medical management. Check films on 2-28-46 showed improvement in the previous deformity, which persisted, however. Peristalsis was regular in rate and tone.

Treatment. A gastric drip of protein hydrolysate and milk and cream mixture was instituted, as in Case I. It was continued for 7 days, then replaced by 3 bland meals and intravenous hydrolysate (500 cc. t.i.d.). The routine antispasmodics, antacids, and sedatives were also employed.

Results. Ten days after therapy had been started, roentgenologic reexamination revealed the behavior of the stomach and duodenal bulb to be normal, and there was no evidence of the previous ulcer. Symptoms had been absent since institution of the gastric drip. Contrary to the usual findings, the patient's weight had dropped from 163.5 to 163.0 pounds.

Total serum protein levels were determined daily during gastric drip treatment and showed a rise from 5.0 to 6.2 grams per cent.

The stomach contents were aspirated at various times while the gastric drip was

running. Before treatment had been started, analysis revealed 53 units of free acid and 66 units of total acidity. Subsequent aspirations were performed 30 minutes after temporarily discontinuing the drip. They averaged 0 units of free acid and 69 of total acidity during the administration of milk and cream. While protein hydrolysate was being given, the values varied from 0 to 34 units of free and from 50 to 71 units of total acidity.

Follow-up. Repeat roentgenograms have not yet been taken, but 1 month after discharge the patient felt fine and had been completely symptom-free.

Case XIV. E. R., 41 year old white female. Occupation: housewife.

Ulcer History. The patient suffered from a "nervous breakdown" in 1940. Following recovery from this she had frequently complained of dyspepsia, but nothing more alarming had developed. On 1-17-46, however, she suddenly developed severe epigastric pain, which later became generalized and radiated to the back and right shoulder blade. It was colicky in nature and occasionally radiated down the left arm. The patient repeatedly vomited undigested food and bile, this temporarily relieving her pain and nausea.

She was a difficult diagnostic problem. After the possibilities other than peptic ulcer had been ruled out, however, a gastrointestinal series was ordered, despite the patient's inability to retain food and the history of a negative series four months before.

X-ray Findings. Studies performed on 1-21-46 revealed marked hyperistalsis and spasticity of the stomach. A filling defect was noted on the greater curvature side of the pyloric end of the stomach close to the pyloric ring. The duodenal bulb had a normal contour and filled and emptied freely. At 6 and 8 hours there was a large gastric retention. The diagnosis was pre-pyloric ulcer and gastric retention; the latter due to fatigue of the gastric musculature secondary to prolonged pylorospasm.

Treatment. Because of the patient's inability to retain the Levine tube, protein hydrolysate was given solely by venoclysis. Five hundred cc. was administered three times daily for 7 days and supplemented by hourly feedings of milk and cream, which she managed to retain. Suitable sedatives, antacids, and antispasmodics were prescribed.

Results. Symptomatic relief was delayed as compared with the results obtained by gastric drip technique. The patient did not vomit, however, once hydrolysate had been started, and in two days she complained only of slight epigastric pain and tenderness. From the third day on, she was completely symptom-free.

This is one of two cases which developed side reactions to protein hydrolysate administration. Frontal headache, facial flush, and general malaise developed if the venoclyses exceeded the rate of 50 drops per minute. The ulcer disappeared, nevertheless, and the total serum protein rose from 6.2 to 7.0 grams per cent during treatment. Fluoroscopic and film studies showed normal gastro-duodenal activity, no evidence of the previous prepyloric filling defect, and no gastric retention at six hours.

Follow-up. Roentgenograms 7 weeks after hospital discharge revealed the stomach and duodenal bulb to continue to have a normal appearance. The patient had occasional periumbilical pain, but this had no time relation to eating and was relieved by passage of flatus.

SUMMARY OF RESULTS

In 9 of the 15 cases included in this study the ulcer deformity completely disappeared, according to the roentgenograms taken immediately after therapy. Five cases showed marked improvement by X-ray, one of these (Case V) displaying complete disappearance of his duodenal deformity 11 weeks later. Case XV failed to improve. In general, the older the patient and the longer his ulcer history, the less rapid and complete his roentgenologic recovery.

Of the 14 cases which improved, none had evidence of crater formation after treatment. Case V, one of 3 with a 6-hour gastric retention, had a slight retention at the time of hospital discharge, but studies 11 weeks later revealed complete resolution of the duodenal deformity and a normal rate of gastroduodenal emptying.

Four patients had hematemesis and melena just prior to admission, but further bleeding did not occur once treatment was instituted. Case XIII had a duodenal ulcer according to admission roentgenograms, but check films following therapy revealed a small deformity on the lesser curvature of the stomach. This had previously been obscured by marked gastric dilatation and rotation, which subsided as the duodenal ulcer and associated pylorospasm cleared up. Whether this gastric deformity was a cicatrix or an ulceration could not be determined, but the absence of symptoms made the former more probable.

Case XV failed to respond to treatment. A 52 year old white male with a 15-year history of intermittent urticaria and migraine, he entered the hospital because of a mild diabetes, which was easily controlled. Nausea and vomiting developed, and subsequent studies revealed a duodenal ulcer associated with severe gastritis. Intravenous treatment was elected because the patient could not retain a Levine tube, but 15 days of this were ineffective. The ulcer was thought to be secondary to an elevated histamine level accompanying his allergic state, which was not under control.

The average course of protein hydrolysate lasted 9 days. X-ray check studies were performed immediately thereafter. Total serum proteins were determined in 11 cases, the average value before therapy being 5.3 gm. per cent, and that after therapy 6.2 gm. per cent, representing an average rise of 0.9 gm. per cent in 9 days. The average weight gain for 12 patients was $1\frac{3}{4}$ pounds, but values varied from plus $6\frac{3}{4}$ to minus 5 pounds.

All except Case XV were rendered completely free of ulcer symptoms during treatment. Drip feeding usually accomplished this immediately but occasionally required 12 hours. Intravenous hydrolysate at times afforded complete relief within 12 hours but ordinarily required 48 hours, and in one case (III) 96 hours.

Side reactions were infrequent. No cellulitis or phlebitis was encountered incident to hydrolysate venoclysis. Case I vomited when receiving 1500 cc.

uninterruptedly by gastric drip, but this disturbance was eliminated by alternating 500 cc. of protein hydrolysate with 600 cc. of milk and cream. Another individual (XIV) developed a frontal headache, facial flush, and nausea, but only when the venoclysis exceeded 50 drops per minute. No other side reactions attributable to protein hydrolysate were noted in administering 205 litres of the product.

Follow-up and control studies are not yet complete, the investigation having

TABLE IV

CASE	AGE	ULCER HISTORY	COMPLICATIONS	TREATMENT		X-RAY IMPROVEMENT	SYMPTOMATIC RELIEF*	SERUM PROTEIN ELEVATION	WEIGHT GAIN
				Mode	Duration				
					days			gm. %	lbs.
I	37	3 yr.	hematemesis	drip	7	complete	complete	4.1-5.5	3
II	36	15 mo.		drip	7	complete	complete		4
III	39	4 da.		i.v.	10	complete	complete		
IV†	64	4 yr.	retention	com.‡	9	complete	partial	6.0-6.0	-1
V	69	15 yr.		drip	7	marked	complete	5.5-6.7	4
VI†	30	5 yr.		drip	7	marked	complete		-5
VII†	49	8 yr.		drip	7	complete	complete	5.9-6.2	1
VIII†	56	4 mo.		com.	9	marked	complete		1
IX	35	2.5 mo.	hematemesis	i.v.	10	complete	complete	5.4-6.2	1½
X†	31	10 mo.		com.	10	complete	complete	5.0-6.0	½
XI†	44	10 mo.		com.	9	marked	complete	7.2-7.8	1½
XII	34	4 yr.		com.	12	marked	partial	4.3-5.6	6¾
XIII	42	1 yr.		com.	9	complete	complete	3.2-5.5	5
			and retention						
XIV	41	4 da.	vomiting and retention	i.v.	7	complete	complete	6.2-7.0	
XV	52	1 wk.	vomiting	i.e.	15	none	none	6.0-6.0	

* Symptomatic relief refers to period following hospitalization. All but case XV were completely relieved during treatment.

† Intractable cases.

‡ Com. = combined

been started only 8 months ago. So far, however, no case in which X-ray evidence of the ulcer completely disappeared has had a recurrence. Only one of this group (IV) is having symptoms, these being intermittent and mild. Patients who were roentgenologically markedly improved have remained so, or shown even further recovery on subsequent studies. Case XV, who did not respond to treatment while hospitalized, later improved, but there probably was little connection between therapy and his subsequent symptomatic recovery. Finally, all serum proteins have maintained or exceeded the level at the time of hospital discharge.

An analysis of individual cases appears in Table IV.

SUMMARY AND CONCLUSIONS

Thirteen cases of duodenal ulcer, 1 of gastric ulcer, and 1 of combined duodenal and gastric ulcer are presented. A 6 per cent solution of protein hydrolysate was administered by gastric drip or venoclysis, 1500 cc. being given daily for an average of 9 days.

In 9 cases, X-ray evidence of ulcer disappeared. Five cases showed marked improvement, one of these clearing up completely in 11 weeks. One patient failed to respond to treatment. It is believed that protein hydrolysate is effective in treating the ulcer patient because it neutralizes gastric acid and adds to the supply of body protein.

Follow-up and control studies are being undertaken to confirm the long range value of protein hydrolysate in peptic ulcer therapy.

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PROTEIN HYDROLYSATE THERAPY FOR PEPTIC ULCER

REPORT ON 26 CASES

HORACE H. HODGES, M.D.¹

*From the Gastro-Intestinal Section (Kinsey-Thomas Foundation) of the Medical Clinic,
Hospital of the University of Pennsylvania.*

INTRODUCTION

In view of the current wide-spread interest in protein metabolism and of the therapeutic use of amino acids in various diseases, it is not surprising that a protein hydrolysate has been tried in the treatment of peptic ulcer. Unfortunately its apparently beneficial effect, before being confirmed by adequate clinical experience, has been widely publicized in the lay press. Co Tui and his associates (1), however, have reported favorably on the use of such hydrolysates in 26 cases of this disease and have suggested that the beneficial effect may be due to the buffering action of the amino acids and a high nitrogen intake. Their impression has been supported by that of Schenker and Clark (2), who, however, used the hydrolysate only as a supplement to a bland diet in the pre-operative management of 55 ulcer patients. They reported prompt relief of symptoms and, at operation, a reduction of gastritis, duodenitis, edema and hyperemia. More recently, Vinci and his associates (3) have advocated a high protein, high caloric diet, in which a protein hydrolysate is the principal source of nitrogen. On such a program, which included hospitalization and "almost complete" bed rest, they reported many of their 30 patients "clinically and radiographically free of ulcer" after 18 to 21 days. Eight patients in this series, however, required surgical intervention primarily because of the manifestations of intractable ulcer.

The purpose of the study reported in this preliminary communication has been to evaluate critically the effectiveness of the oral administration of a protein hydrolysate in the treatment of chronic peptic ulcer and to make certain observations pertaining to nutrition and metabolism in human subjects whose sole source of dietary nitrogen was pre-digested protein.

SUBJECTS

Since February, 1946, 26 patients have been selected for this study, primarily on the basis of the chronicity of their ulcers. Twenty-four had received adequate conventional dietary therapy previously on an ambulatory basis without significant improvement or had suffered a recurrence of symptoms while adhering to such a program. One of these, in addition, received rigid dietary man-

¹Resident in Medicine and Fellow in Gastroenterology. Present address 117 W. 7th St. Charlotte 2, N.C.

TABLE I

Pertinent data relative to patients before initiation of hydrolysate therapy and the general results of the therapy

CASE NO.	AGE AND SEX	LOCATION OF ULCER	DURATION OF ULCER SYMPTOMS	ULCER MANIFESTATIONS			ROENTGEN AND ENDOSCOPIC APPEARANCE BEFORE TREATMENT	DURATION OF HYDROLYSATE THERAPY	DURATION OF PAIN AFTER BEGINNING TREATMENT	ROENTGEN AND ENDOSCOPIC APPEARANCE AFTER TREATMENT	FOLLOW-UP OBSERVATIONS
				Pain	Bleeding	Retention vomiting					
1	56 M	D	3 yrs.	6	2+	0	Crater, irritability	16 days	7 days	No evidence* of active ulcer	Recurrence after 5 weeks. Vagotomy
2	30 M	J	2.5	4+	0	0	Penetrating crater just distal to the stoma	2		Not done	Vagotomy
3	31 M	D	5	1+	3+	0	Crater, irritability	14	1	No evidence of active ulcer	No recurrence in 8 months
4	40 M	J	0.8	4+	0	0	Penetrating crater just distal to the stoma	19	9	No evidence of active ulcer	No recurrence of symptoms and radiographically negative after 6 mo.
5	45 M	G	0.3	4+	0	0	Penetrating crater, 2 x 2 cm., lesser curvature of antrum	21	2	No evidence of active ulcer	No recurrence in 2 mo.
6	32 M	D	13	3+	0	1+	Crater, "cloverleaf deformity". 70% gastric retention at 3 hours	21	1	Deformity persists. No crater seen. 10% retention at 3 hours	Gastric resection for residual pyloric obstruction
7	63 M	J	2	3+	1+	0	Bleeding crater just distal to the stoma seen by gastroscope. Not seen radiographically	21	5	No evidence of active ulcer. Gastrosocopy unsatisfactory	No recurrence in 6 mo.
8	47 M	D	1.5	3+	0	0	Deformity, irritability and questionable crater	19	8	No improvement	Recurrence after 3 weeks
9	49 F	D	2.5	3+	0	0	Crater, irritability	15	4	No evidence of active ulcer	Recurrence after 5 mo.
10	37 M	G	5	2+	0	0	Crater, 5 x 7 mm., lesser curvature	14	1	No evidence of active ulcer	Gaseous indigestion after 4 mo. Radiographically negative after 5 mo.
11	18 F	D	1.5	2+	0	0	Crater, irritability and moderate gastric retention	19	1	Irritability, no crater. 5% gastric retention at 3 hours	No recurrence in 4 mo. Further radiographic improvement
12	36 M	D	9	2+	0	0	Crater, irritability	19	4	No evidence of active ulcer	No recurrence in 3 mo.
13	48 M	D	22	4+	0	0	Irritability, spasm and questionable crater	19	4	No improvement	Recurrence after 1 week. Vagotomy

TABLE I—Continued

CASE NO.	AGE AND SEX	LOCATION OF ULCER	DURATION OF ULCER SYMPTOMS	ULCER MANIFESTATIONS			ROENTGEN AND ENDOSCOPIC APPEARANCE BEFORE TREATMENT	DURATION OF HYDROLYSATE THERAPY	DURATION OF PAIN AFTER BEGINNING TREATMENT	ROENTGEN AND ENDOSCOPIC APPEARANCE AFTER TREATMENT	FOLLOW-UP OBSERVATIONS
				Pain	Bleeding	Retention vomiting					
			yrs.					days	days		
14	46 M	D	5	4+	0	0	Crater, irritability	10		Not done	Gastric resection
15	29 M	D	3	1+	0	0	Crater, irritability	21	1	No evidence of active ulcer	Recurrence after 1 mo.
16	49 F	D	7	2+	0	0	Crater, irritability	21	2	No evidence of active ulcer	No recurrence in 4 mo.
17	49 M	D	3	1+	1+	0	Crater, spasm	21	2	No improvement	Recurrence after 2 mo. Gastric resection
18	55 M	D	11	3+	0	1+	Pyloro-duodenal spasm. 70% gastric retention at 3 hours	20	2	Irritability. No gastric retention at 3 hours	Recurrence after 4 mo.
19	51 F	D	18	3+	0	0	Crater, irritability. Moderate gastric retention at 3 hours	21	5	No evidence of active ulcer	No recurrence in 1 mo. Radiographically negative
20	39 M	D	10	4+	0	0	Two craters, irritability	21	20	Irritability. One questionable crater	Recurrence after 6 weeks
21	34 F	G	10	2+	0	0	Crater on lesser curvature. Antral spasm. 60% gastric retention at 3 hours	21	4	Antral spasm but no crater. No gastric retention at 3 hours. Gastroscopy negative	No recurrence in 1 mo.
22	52 M	D	20	3+	3+	0	Crater, spasm	6		Not done	Vagotomy
23	48 M	D	1	3+	0	0	Two craters, irritability	21	2	Irritability, no crater	No recurrence in 1 mo.
24	32 M	D	7	4+	0	0	Penetrating crater, spasm	21	10	Decreased spasm, questionable crater	No recurrence in 1 mo.
25	51 M	E	2	2+	0	0	Crater near cardia. Congenital short esophagus. Small hiatal hernia. Esophagoscopy unsatisfactory and followed by mediastinitis	21	1	Cardio-spasm, no crater	No recurrence in 1 mo.
26	48 F	G	1.5	3+	0	0	Crater, 1.5 x 1 cm., lesser curvature	21	4	No evidence of active ulcer. Gastroscopy revealed a healed scar	No recurrence in 1 mo.

* No crater or secondary evidence of an ulcer was demonstrable, although deformity due to scarring may have been present.

agement in the hospital for two weeks prior to the institution of the hydrolysate therapy. The 2 others (Nos. 5 and 10, Table I) had not been adequately treated in the usual manner, but were included because each had a chronic gastric ulcer, the crater of which was nicely demonstrable in profile by roentgenogram, thus affording an opportunity to observe variations in its size with the progress of the therapy. This rather strict selection of subjects accounts for the relatively small number employed.

Twenty-three of the patients were hospitalized for the entire course of treatment. Two (Nos. 10 and 25) were hospitalized for an initial 4 and 7 days, respectively, and thereafter continued the treatment on an out-patient basis. One patient (No. 15) was treated entirely on an out-patient basis, being allowed to continue his work as resident physician in the hospital. All hospitalized patients were allowed as much activity as they desired throughout the treatment period.

The pertinent data regarding these patients are given in Table I. Twenty were males, 6 females. The ages varied from 18 to 63 years. Eighteen had a duodenal, 4 a gastric, 3 a gastro-jejunal (stomal) and 1 an esophageal ulcer. The duration of symptoms ranged from 4 months to 22 years. Five patients exhibited prolonged gastric retention by roentgen study. Two were suffering from retention vomiting at the time the hydrolysate therapy was initiated. Three patients had had a recent hemorrhage and 1 was bleeding slowly at the beginning of the treatment. Five had clinical and roentgenological evidence of deep penetration and (or) threatening perforation.

In each patient, the symptoms and physical observations indicated clearly a diagnosis of active peptic ulcer. Except in 3 instances, this diagnosis was radiographically confirmed very shortly before or at the onset of hydrolysate therapy. Gastroscopy demonstrated a gastro-jejunal ulcer immediately prior to treatment in 1 of these exceptions. The second had had repeated roentgen study over a period of 18 months, all showing a large duodenal crater and moderate gastric retention. Though the last such examination had been done 3 months before the hydrolysate therapy, she had shown no symptomatic improvement; on clinical grounds, no doubt existed as to the presence of an active ulcer. The third patient who was not radiographed immediately before treatment had had a gastroenterostomy for an intractable duodenal ulcer in 1934 and repeated episodes of hemorrhage and ulcer pain had occurred since that time. Three months before treatment, a crater in the duodenal cap had been demonstrated radiographically. He was having intractable pain and had suffered a large gastro-intestinal hemorrhage only two days before the institution of the hydrolysate therapy. All patients except Nos. 2, 14 and 22, in whom treatment was discontinued prematurely because of a complication or of failure to respond satisfactorily, were re-examined roentgenologically after 14

to 21 days of therapy. Follow-up gastroscopic examinations were done in appropriate cases.

TREATMENT PROGRAM

The therapy consisted of the frequent administration of an equal mixture of "protolysate and dextri-maltose" (Laboratory Product No. 197³). Between 650 and 800 gm. of this mixture, dissolved in 2000 to 2400 cc. of water, depending on the size of the patient, were administered daily. Divided feedings were given as frequently as necessary to control symptoms, but at least every 2 hours while awake. The average sized patient ingesting 750 gm. of this mixture daily was provided the nitrogen equivalent of 285 gm. of protein, about 2900 calories, and about 7.5 gm. of sodium chloride.

Protolysate (formerly called "amigen") is an enzymatic hydrolysate of casein, which, according to the manufacturer, contains 12 per cent total nitrogen, 65 per cent of which is amino nitrogen. It is said that each gm. yields 3.7 calories and is equivalent in nitrogen content to 0.76 gm. of protein. The content of sodium and of chlorine, each, is given as 1.5 per cent. The content of iron and other important minerals, according to the manufacturer's analysis, is such that a daily intake of 650 to 800 gm. of the mixture meets the optimal mineral requirements given by Rose (4). The dextrimaltose is considered to have no special value other than that of supplying carbohydrate and calories (3.9 calories per gm.).

Except in 4 instances, no other food material was allowed during the treatment period of 14 to 21 days, but adequate vitamin supplements were provided routinely. These 4 patients received 15 to 30 cc. of light cream or vegetable oil with each 2-hour feeding in an effort to decrease the speed of gastric emptying. Syntropan and gelusil were allowed during the first 5 days in the treatment of 1 patient. Syntropan was inadvertently administered throughout the treatment period in another. Iron was administered only in the presence of an appreciable anemia. Toward the end of the study, it became the practice to continue for 3 to 6 weeks after resumption of a bland diet the administration of 100 gm. of protolysate daily in the form of interval feedings.

RESULTS

Symptomatic: Complete relief of symptoms was obtained in 23 patients in an average of 4.4 days (Table I). These patients from the start uniformly experienced more complete and longer relief from pain following the individual protolysate-dextrimaltose feedings than they had previously received from milk and cream or other bland foods. Retention vomiting disappeared almost

³ Supplied through the courtesy of Dr. Warren M. Cox, Jr., of The Mead Johnson Company.

immediately. Six of them required feedings more frequently than each second hour for the first few days.

The remaining 3 patients failed to respond symptomatically or were actually worse. In them the treatment was discontinued after 2, 10 and 6 days respectively: in one (No. 2), because a perforation was feared; in the second (No. 14), because of a massive gastro-intestinal hemorrhage; and in the third (No. 22), because of the failure to obtain symptomatic relief.

TABLE II

The effect of protein hydrolysate therapy on body weight, blood urea nitrogen, serum protein and hemoglobin

CASE NO.	WEIGHT CHANGE	BLOOD UREA N ₂		SERUM PROTEIN		HEMOGLOBIN	
		Before therapy	At end therapy	Before therapy	At end therapy	Before therapy	At end therapy
	lbs.	mgm. %	mgm. %	gm. %	gm. %	gm. %	gm. %
1	+3	12	23	6.4	6.8	82	80
2	-2	12	12	7.1	6.8		
4	0	13	22	6.1	6.1	50*	50
5	+4	12	12	7.9	6.1	86	86
6	+2	17	31	7.2	6.4	80	77
7	+6	12	15	6.7	6.1	62	72
8	+8						
9	+4					83	81
10	+1						
11	+4						
12	+4					100	75
13	+3	24	15	6.4	7.7		
15	0	11	18	6.9	6.7		
16	+7	10	12	6.3	6.5		
17	+7	19	21	7.1	6.0	49*	48
18	+10			7.2	6.5	48*	47
19	+14	10	14	7.0	6.0	67*	66
20	+5	24	24	6.4	6.2	90	96
21	+9	7	11	7.0	7.2	65*	71
22	+3	14	17	5.7	6.8	55*	64
23	+5	17	21	6.7	6.5	101	100
24	+4			6.7	6.8	103	94
25	+2	17	27			74	84
26	+5	10	22	7.3	6.9	74	65

* Ferrous sulfate administered orally.

Roentgen observations: Of the 23 patients who became asymptomatic, 12 showed no roentgen evidence of ulcer activity after the 2 to 3 weeks' treatment period. Eight showed marked improvement but with some residual irritability, spasticity and (or) deformity and no demonstrable craters. In 3 there was no radiographic evidence of improvement.

The amount of barium retained in the stomach at the end of 3 to 4 hours was

markedly reduced in every instance. A marked degree of gastric retention seen in 2 patients before treatment entirely disappeared (Fig. 1).

Nutritional and metabolic observations: A gain in weight was the rule, the average being 4.5 pounds (Table II). A single patient lost weight in the amount of 2 pounds, and 2 patients exhibited no weight change. The maximal gain was 14 pounds in 3 weeks.

Ten of 11 patients on whom accurate intake-output records were obtained showed an appreciable diuresis during the last few days of treatment and (or) the 2 to 3 days immediately following resumption of an ordinary bland diet. With the diuresis, a loss of weight averaging 2.8 pounds occurred. This was noted usually in the patients whose weight gain had been above the average so that the majority maintained a net gain varying from 3 to 10 pounds. Also contributory to the weight loss was the fact that the majority of the patients were fasted an average of 25 of the first 48 hours after termination of the treatment in preparation for a gastric analysis and a gastro-intestinal roentgen study.

A serum protein determination was done on 18 patients immediately before and upon completion of treatment (Table II). In only 1 was the initial value below 6 gm. per cent. Six patients gained an average of 0.55 gm. per cent, while 11 lost an average of 0.66 gm. per cent. No change was noted in the other. No serum protein value declined below 6 gm. per cent. In 1 (No. 22), the serum protein level rose from 5.7 to 6.8 gm. per cent after only 6 days of hydrolysate therapy.

A blood urea nitrogen determination was likewise made on 17 patients. The initial value was elevated slightly in 3 patients who had received hydrolysate feedings for 24 hours before the determination. No evidence of impaired renal function was present in these patients. Thirteen patients exhibited an increase during the treatment period averaging 6.5 mgm. per cent. In several instances the blood urea nitrogen was found higher about mid-way of the treatment period than at the end, suggesting some adaptability on the part of the body to handle this excess urea.

The effect of the hydrolysate therapy on hemoglobin is shown in Table II. Nine patients showed an anemia varying from 48 to 74 per cent of hemoglobin. Four of these exhibited a rise of hemoglobin, with or without supplementary iron during the treatment. Five showed no rise. A rapid increase in hemoglobin was noted after resumption of a bland diet including meat in 2 of the patients who had shown no rise during the hydrolysate therapy. Excluding Case 14, which developed bleeding, only 1 patient (No. 12) exhibited an appreciable decline in hemoglobin. This remains unchecked and, if accurate, unexplained.

Gastric acidity: Fractional gastric analysis, using a test meal of oat-meal gruel, was performed under comparable conditions immediately before and at the termination of the treatment in 10 patients. The acid secretory response to this stimulant after treatment, as compared to that before, was decreased in 6, increased in 2 and unchanged in 2.

The immediate effect of protolysate-dextrimaltose feedings on gastric acidity was determined 18 times in 14 patients (Table III). The technic of the ordi-

TABLE III

The effect of individual feedings of protolysate and dextrimaltose mixture on gastric acidity in 14 cases of peptic ulcer

CASE NO.	FREE HYDROCHLORIC ACID								
	Fasting	Minutes after protolysate-dextrimaltose feeding							
		15	30	45	60	75	90	105	120
6	42	0	0		22		66		84
8	38	0	0	0	0		10		28
10	0	0	0	0	0	0	0	0	0
11	8	0	0	0	0	0	0	6	18
12	26	0	0	0	0	54	60	42	62
	28*	0	0	0	0	4	20		26
13	82	0	0	0	10	60	90	102	110
							24†		36†
14	42	0	0	26	60		60		68
	26*	0	0	0	0		72		84
15	0	0	0	0	0	16	46		62
16	38	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	28	24
18	56	0	0	0	0	32		44	52
19	4	0	0	0	0	8	10		18
21	20	0	0	0	0	0	16		42
23	30	0	0	0	0	0	0	0	48

* Determinations begun 2 hours after the last of a series of 2-hourly feedings.

† Single determination 2 hours after the last of a series of 2-hourly feedings.

‡ Single determination 1½ hours after the last of a series of 1½-hourly feedings.

nary fractional gastric analysis was employed except that a single feeding, containing 60 to 70 gm. of protolysate-dextrimaltose mixture in 200 cc. water, was substituted for the oat-meal gruel. In every instance the gastric content was immediately rendered free of ionizable hydrochloric acid as measured by Topfer's reagent. Free hydrochloric acid remained absent for an average of 70 minutes, the range being 30 to 120+ minutes. In general it was noted that the time for reappearance of free acid was proportional to the rapidity of gastric emptying. In other words, free acid was absent longest in stomachs which emptied slowest. It was also noted that free acid was absent longer after the

last of a series of 2 hourly feedings than after the first feeding of the day when the patient had fasted overnight. Consequently, the majority of the patients had no free acid in their stomachs for more than half the waking hours and a reduced amount for the remainder of the time.

Complications and difficulties encountered: A single major complication developed during our experience with the hydrolysate therapy, this being a serious gastro-intestinal hemorrhage on the 10th day.

Diarrhea appeared in 2 patients. In 1 it persisted at the rate of 5 to 6 small liquid stools daily, in spite of the administration of bismuth subcarbonate, 1 gm., 4 times daily. The other case of diarrhea was transient and required no treatment. As a rule bowel movements were less frequent and less voluminous than usual for the individual patient.

Though the taste of protolysate is somewhat unpleasant, no real difficulty was encountered on that account. All the patients ceased to object to the taste after 24 to 48 hours. It is interesting, however, that this mixture, in spite of supplying an adequate caloric and nitrogen intake, did not satisfy the normal sensation of hunger.

It is perhaps noteworthy that no patient developed any clinical manifestation which might have been attributed to a diet entirely devoid of fat.

FOLLOW-UP OBSERVATIONS

Of the 20 patients in whom roentgen evidence of healing or improvement occurred, 5 had a recurrence of ulcer symptoms within 1 to 5 months after termination of the therapy. One was subjected to a gastric resection, in spite of the absence of recurrent ulcer symptoms, because of partial pyloric obstruction. Fourteen have remained asymptomatic for 1 to 8 months. In no instance has a gastric ulcer recurred.

All 3 patients, who exhibited no improvement radiographically, subsequently had a prompt return of ulcer symptoms which necessitated surgical treatment. The 3 patients who failed to respond symptomatically have also been subjected to operation.

COMMENT

An accurate evaluation of the results from the hydrolysate therapy in this series is difficult and largely a matter of clinical impression. Three "failures" occurred in the 26 patients, but the majority of them made a more satisfactory response to the protein hydrolysate therapy, administered in the hospital, than they had previously made to ambulatory conventional management. There can be no doubt regarding the beneficial effect of hospitalization per se in peptic ulcer. It was to minimize this factor that the patients were not confined to bed at any time. Also, in 2 patients, the factor of hospitalization does not enter

into the comparison, and in these the protein hydrolysate therapy proved to be the more efficacious. In several other instances, the prompt relief of symptoms and the roentgenologic demonstration of rapid healing of a large crater and of the disappearance of gastric retention was dramatic (Nos. 4, 5, 7, 18, 21, 23, 25 and 26, Table I; Figs. 1 to 6). The patient with an esophageal ulcer deserves special comment since peptic ulceration in this area is uncommon and usually quite refractory to medical management. Relief of symptoms was immediate and a roentgen examination after three weeks of the treatment indicated that the ulcer had healed.

A rough comparison of the immediate results presented in this paper may be made with results reported by Cummins, Grossman and Ivy (5) in a study of "healing time" of craters in 63 cases of duodenal and six cases of gastric ulcer. On energetic hospital management, an average of 40 days was required for the disappearance of a duodenal ulcer crater by roentgen examination and an average of 42 days for a gastric crater. It should be noted, furthermore, that the majority of their patients had had ulcer symptoms less than 12 months and their cases were not regarded as intractable.

In regard to the prevention of a recurrence of peptic ulcer, our data suggest that the protein hydrolysate therapy, administered over a relatively short period of time, was no more efficacious than any of the conventional dietary programs.

Observations by many other investigators (1, 6-12), have adequately demonstrated that protein hydrolysates, constituting the sole source of dietary nitrogen, compare favorably with good food protein in supporting growth, nitrogen balance and plasma protein and hemoglobin regeneration both in the human and in animals. Such hydrolysates, however, being composed largely of amino acids, require little further digestion and are absorbed more rapidly and completely from the intestinal tract than is native protein (13). The prolonged acid-neutralizing action has also been previously noted (1, 14).

The inconsistencies in respect to serum protein and hemoglobin levels observed before and after treatment in this study may be more apparent than real. Unfortunately, simultaneous hematocrit or blood volume determinations were not made. Co Tui et al., however, made observations regarding the plasma proteins before and after hydrolysate treatment, and noted a decline in the hematocrit values. They suggested that an initial hemoconcentration with subsequent restoration of normal blood volume or an over-hydration might explain the variations. The intake-output and weight records of the patients in this study support such an explanation.

The consistent rise in the blood urea nitrogen level is somewhat puzzling, but suggests that the liver is capable of forming urea at a rate in excess of the normal renal excretory capacity.

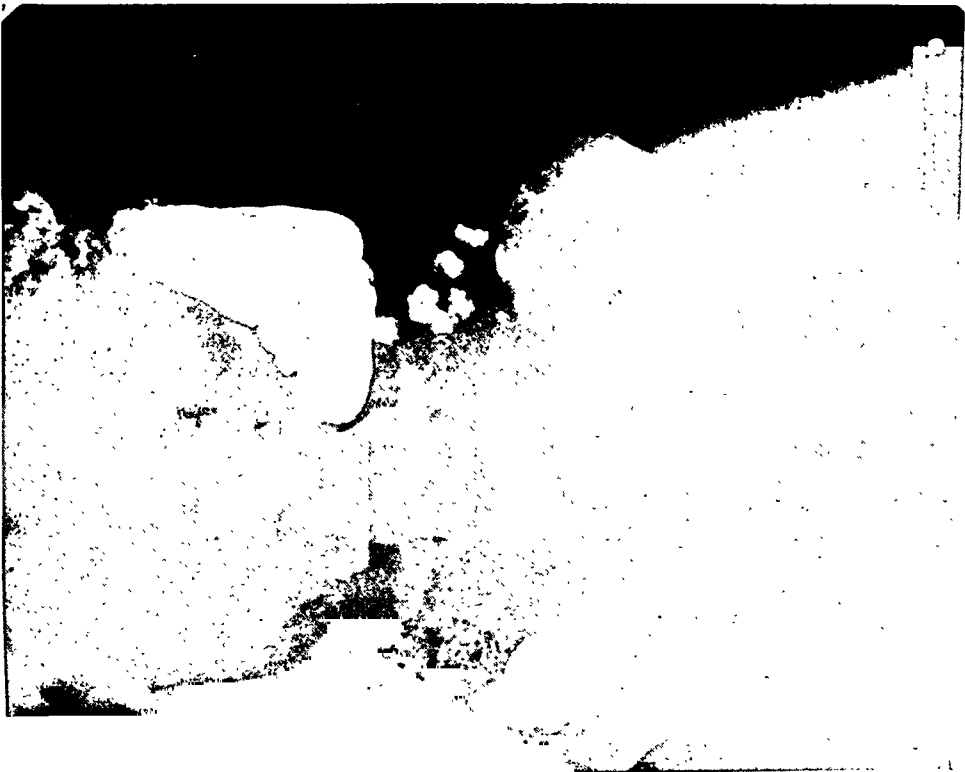


FIG. 1-A. Case 21. Four-hour roentgenogram showing 60 per cent gastric retention.



FIG. 1-B. Case 21. Three-hour roentgenogram after 21 days of hydrolysate therapy showing complete emptying of the stomach.

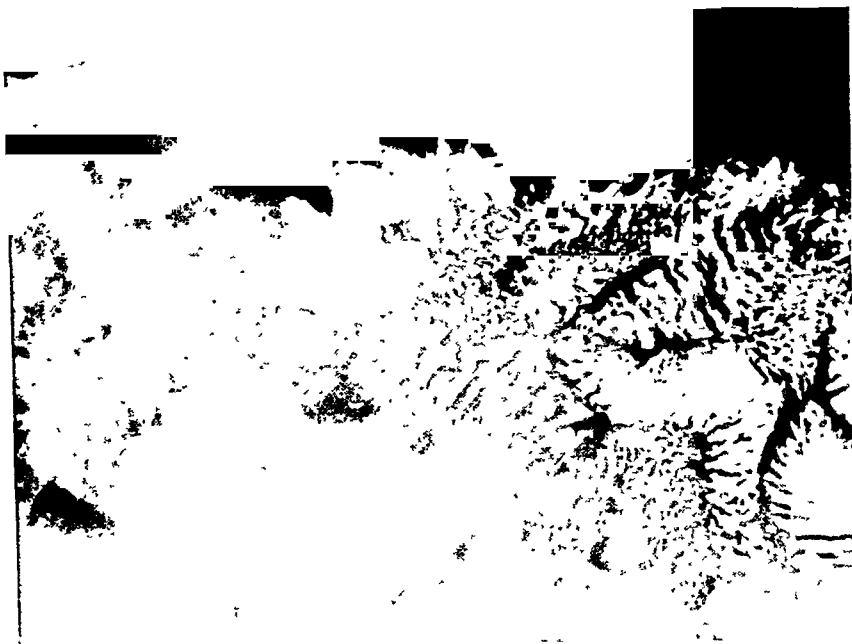


FIG. 2-B. Case 4. Disappearance of the crater after 19 days of hydrolysate therapy.

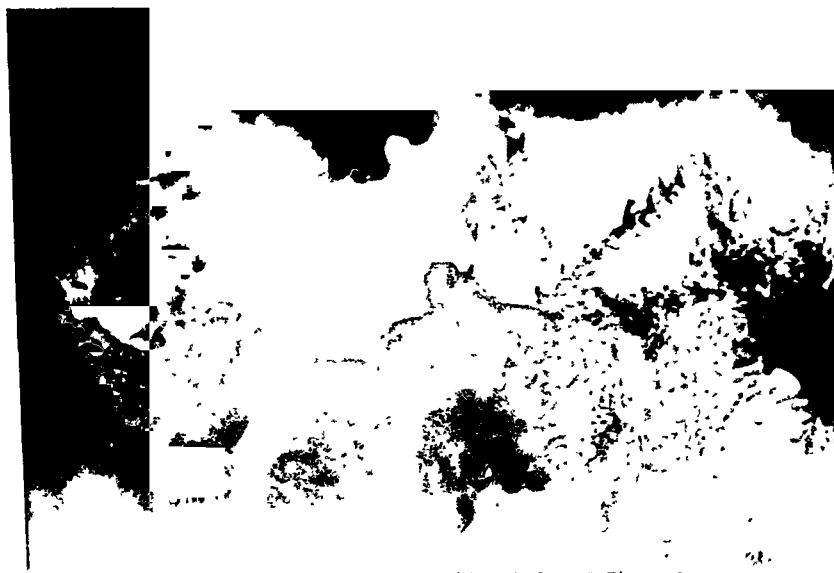


FIG. 2-A. Case 4. Penetrating ulcer of the jejunum just distal to the stomach.



FIG. 3-A. Case 5. Large crater on the lesser curvature of the pyloric antrum.



FIG. 3-B. Case 5. Disappearance of the crater after 21 days of hydropyloric therapy.



FIG. 4-B. Case 23. After 21 days of hydrolysate therapy, the crater has disappeared and the spasm is markedly decreased.



FIG. 4-A. Case 23. Crater and spasm in duodenal cap.

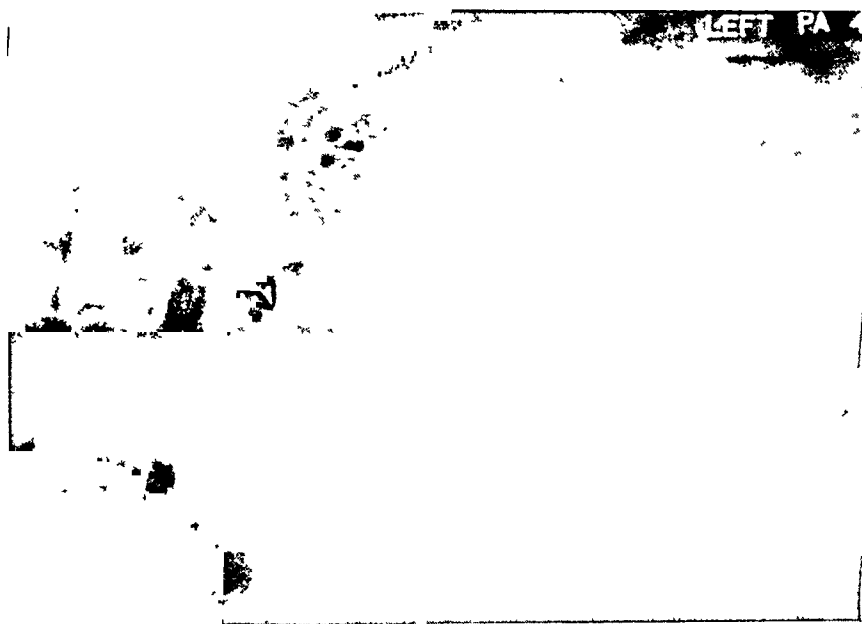


FIG. 5-A. Case 25. Crater in the lower end of the esophagus in a patient with a congenital short esophagus and small hiatal hernia.

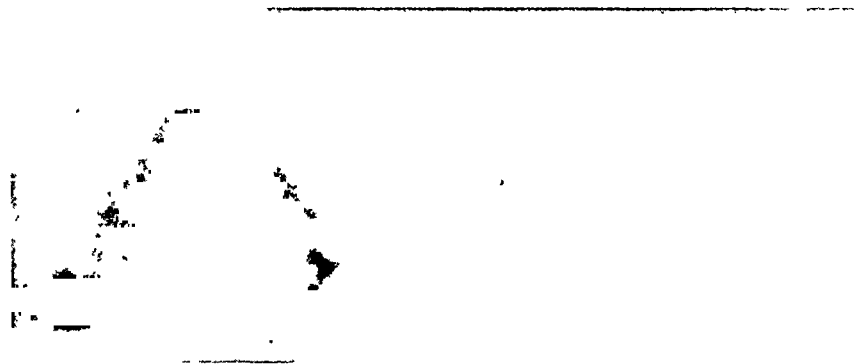


FIG. 5-B. Case 25. Spot-film of the esophageal crater.

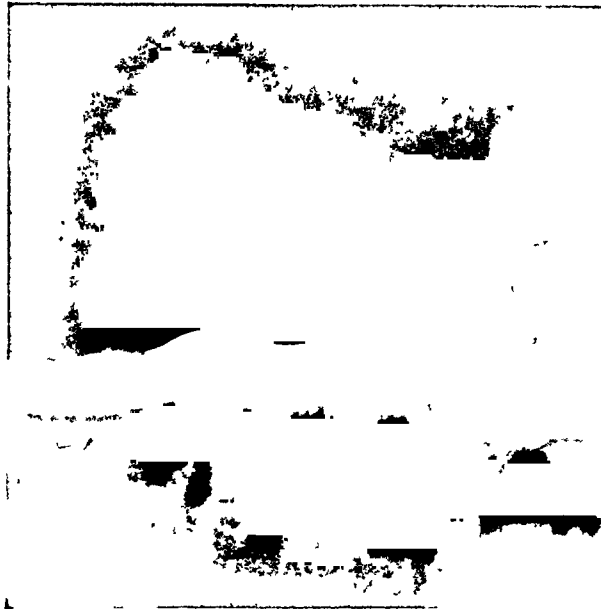


FIG. 5-C. Case 25. After 21 days of hydrolysate therapy, the crater is no longer demonstrable.



FIG 6-B Case 26 Complete disappearance of the crater after 3 weeks of therapy

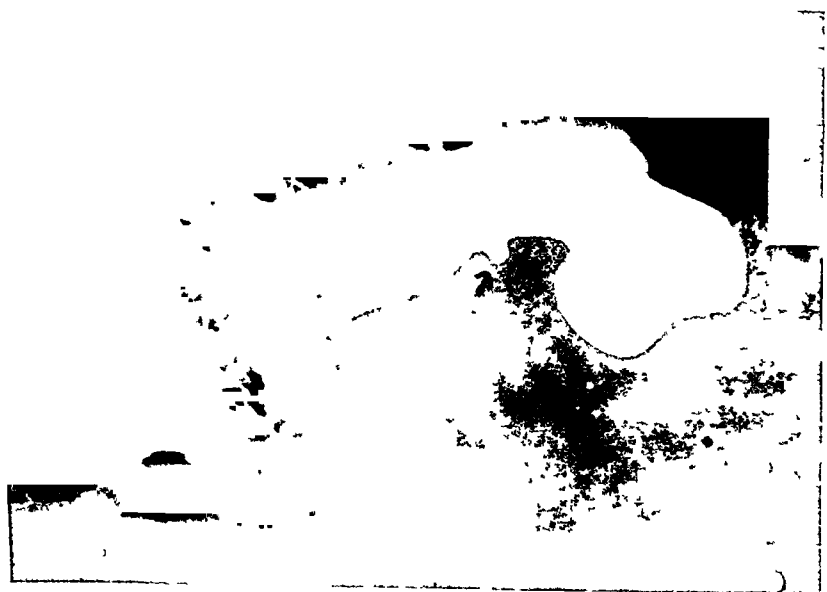


FIG 6-A Case 26 Lesser curvature gastric crater

It will be necessary to observe many more patients before protein hydrolysate therapy for peptic ulcer can be fully evaluated. The present expense of the commercial preparations and of the necessary vitamin supplements precludes its routine use in most cases. It is quite possible, however, that this therapy may prove to be an important adjunct to the dietary management of the refractory ulcer, especially for those in which surgery is contraindicated. Also the rapid healing of the gastric craters suggests that this type of therapy may prove useful as a therapeutic test in ruling out malignancy.

In selecting a protein hydrolysate for clinical use, one should consider especially its protein source, degree of hydrolysis, mode of hydrolysis and content of nitrogen and minerals. Recent reports indicate that acid hydrolysates and synthetic or crystalline amino acids are lacking in some factor ("Strepogenin," Woolley) necessary for maximal growth in animals and certain bacteria (15-18). As this factor is not destroyed by tryptic digestion, it is presumably retained in the various commercial enzymatic hydrolysates.

SUMMARY AND CONCLUSIONS

Twenty-six patients with chronic peptic ulcer were treated with a protein hydrolysate-carbohydrate mixture for a period of 2 to 3 weeks. In the majority, this treatment appeared more efficacious than a conventional dietary program in producing a remission, but the frequency of relapses was not diminished. Three patients failed to respond satisfactorily, one of these suffering a serious gastro-intestinal hemorrhage in the midst of therapy.

A gain in weight was the rule. A rise in blood urea nitrogen was seen in most of the patients but the serum protein and hemoglobin changes were inconsistent.

The degree of gastric acidity after treatment tended to be reduced. Individual feedings of this mixture completely neutralized free gastric acid for an average of 70 minutes.

The beneficial effects of the protein hydrolysate are ascribed to its buffering action and to the high nitrogen intake.

It is believed that the protein hydrolysate may become a useful adjunct to the medical management of peptic ulcer but, as now employed, will not prove to be a panacea.

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NONREACTIVE ALUMINUM HYDROXIDE IN THE TREATMENT OF PEPTIC ULCER

FRANCES H. SMITH, M.D.

Department of Gastroenterology, The Lahey Clinic, Boston, Massachusetts

INTRODUCTION

Although much has appeared in the literature on the use of reactive aluminum hydroxide in the treatment of peptic ulcer, there has been little discussion of the use of nonreactive aluminum hydroxide. The principal difference between these two forms of aluminum hydroxide lies in their reactivity in the presence of hydrochloric acid. The reactive form¹ reacts completely with hydrochloric acid in a relatively short time, while the nonreactive form² remains in the colloidal aluminum hydroxide suspension in the presence of hydrochloric acid for prolonged periods.

This report deals with the use of nonreactive aluminum hydroxide in the treatment of 32 patients with peptic ulcer who were hospitalized but who did not come to surgery between October 1, 1944, and October 1, 1945. Comparison is made with a group of 31 similar cases in which treatment included reactive aluminum hydroxide during the same period. One patient of this group had a gastric resection during a later admission.

BIOCHEMICAL STUDIES

A total of 20 fractional aspirations was done and hydrogen ion determinations made in a group of 7 patients. On the day following admission to the hospital an aspiration was made after fasting. This was immediately followed by an Ewald meal. Aspirations were then made forty-five minutes later and every thirty minutes thereafter for three hours. This procedure was repeated in approximately one week, and again before discharge. In no case was any considerable change observed in the pH or in the shape of the resulting curve.

In 2 patients the contents of three or four aluminoid capsules were added to the Ewald meal. No demonstrable effect resulted from this procedure.

As a laboratory³ means of comparing amphojel and aluminoid, each was titrated, using approximately tenth normal hydrochloric acid. Topfer's reagent was used to indicate the end point. Tenth normal hydrochloric acid was added slowly to 1 cc. of amphojel. An initial end point was noted after

¹ Amphojel is manufactured by John Wyeth and Sons Company.

² Aluminoid was made available for this study through the courtesy of the Chatham Pharmaceutical Co., Newark, N. J.

³ I am indebted to Mr. H. J. Perkin, of the Research Foundation, the Lahey Clinic, for these observations. Many observers have noted that colloidal substances interfere with the obtaining of a sharp end point because of their buffering action. The claim that aluminoid is a more finely dispersed colloid than amphojel would appear to be substantiated by these results.

2.5 cc. of acid had been added. The end point, however, was not permanent and faded within two or three minutes. By repeating this process a final end point was not attained until 13.6 cc. of hydrochloric acid had been added. The whole procedure required approximately one hour to complete. This was considered to be a true end point.

A similar procedure was used with aluminoid. One capsule of aluminoid (5 grains) was dissolved in 10 cc. of water. Tenth normal hydrochloric acid was added in small amounts until an end point was attained which remained permanent for ten minutes. The whole titration procedure required about forty-two hours before a comparable end point was reached. At the final end point, 13 cc. of tenth normal hydrochloric acid had been used. Since 1 cc. of amphojel and 5 grains of aluminoid require the same amount of hydrochloric acid for neutralization, it may be deduced that aluminoid is one twelfth as reactive to hydrochloric acid as is amphojel. This is arrived at on the basis of dry weight of aluminum oxide in the two products. From the above titrations it is also apparent that aluminoid reacts much more slowly with hydrochloric acid than does amphojel.

CLINICAL STUDIES

All patients admitted to the hospital for ulcer management received the following basic treatment after the diagnosis of ulcer was confirmed by x-rays: they were placed at bed rest, given a modified progressive Sippy diet, milk every hour on the hour from breakfast until the evening meal, antispasmodics in the form of small amounts of phenobarbital and belladonna in combination, and high supplementary vitamins. Half of those in the present study received from one to three aluminoid capsules every hour on the half hour from 7:30 a.m. until 7:30 p.m., then every half hour until 9 p.m. If the patient had distress at night, this medication was continued at one to four hourly intervals throughout the night. The remainder of the group was given from 1 to 2 teaspoonfuls of amphojel at similar intervals.

In evaluating the effect of the reactive and nonreactive forms of aluminum hydroxide the data have been divided into subjective and objective findings. To collect the former, each patient admitted for ulcer therapy was provided with a bedside chart which listed the most frequent symptoms occurring in the disease. Opposite these were squares in which he signified the presence or absence of the symptom for each day of the hospital stay. Twenty-eight of the patients were sufficiently cooperative to keep daily records. Ten patients received nonreactive aluminum hydroxide, 10 the reactive form, and 8 received both medications during hospitalization. The symptoms designated occurred on one or more days at any time during the period of hospitalization. The results are tabulated in table 1.

The objective estimation of the efficacy of each of the forms of aluminum hydroxide used was based on: (1) the clinical course, and (2) gastric analyses.

TABLE 1

Subjective Symptoms of 28 Patients on Aluminoid and Amphojel as Recorded During Period of Hospitalization

	ALUMINOID, 10 CASES		AMPHOJEL, 10 CASES		AMPHOJEL		ALUMINOID	
	No.	Per cent	No.	Per cent	8 CASES			
					No.	Per cent	No.	Per cent
Nausea.....	2	20	4	40	2	25	1	12
Vomiting.....	2	20	0	0	0	0	1	12
Headache.....	4	40	4	40	4	50	2	25
Visual disturbance.....	1	10	5	50	0	0	1	12
Bad taste in mouth.....	3	30	9	90	5	62	2	25
Pyrosis.....	5	50	3	30	0	0	1	12
Abdominal discomfort.....	3	30	8	80	7	88	6	75
Gas.....	5	50	8	80	6	75	5	62
Belching.....	4	40	8	80	8	100	6	75
Flatus.....	6	60	8	80	6	75	5	62
Constipation.....	4	40	7	70	6	75	3	37
Vertigo.....	0	0	0	0	1	12	0	0
Pain.....	3	30	8	80	7	88	4	50
Disgust for food.....	0	0	2	20	2	25	2	25

TABLE 2

Comparison of Patients Receiving Aluminoid and Amphojel

	ALUMINOID	AMPHOJEL
Sex		
Females.....	9	8
Males.....	23	23
Age		
Range.....	29 to 71 yrs.	32 to 70 yrs.
Average.....	48.4 yrs.	47.3 yrs.
Lesion		
Duodenal.....	29	31
Gastric.....	1	0
Gastric and duodenal.....	1	0
Pyloric.....	1	0
Duration of illness.....	2 mos. to 27 yrs.	2 mos. to 30 yrs.
Symptoms on admission to hospital		
Severe.....	17	18
Moderate.....	10	12
Minimal.....	4	1
Absent.....	1	0

That the two groups are comparable is shown in the close similarity between them in respect to age, sex, lesion, duration of illness and severity of symptoms. These findings are tabulated in table 2.

The first part of this table is self-explanatory. A detailed analysis of the symptoms occurring in the two groups on admission, at discharge and during the period of follow-up is necessary, however, for an understanding of the clinical course. In classifying the symptoms as severe, moderate or minimal, the following criteria were used: symptoms were said to be severe when there was hematemesis, frequent vomiting, anorexia, frequent or intractable pain, night pain, melena, or persistent weight loss. Moderate symptoms included characteristic epigastric pain relieved by food, milk, and alkali, rare vomiting, and epigastric soreness. Minimal symptoms included heartburn, belching, and occasional mild distress after eating.

It should be borne in mind that symptoms listed under the heading of minimal occur in many other diseases of which the most common are irritable colon and gallbladder disease.

Analysis of Symptoms of Patients Receiving Nonreactive Aluminum Hydroxide

There were 32 patients who received aluminoid therapy. Of these, 17 were admitted with severe symptoms, 10 with moderate symptoms, and in 4 the symptoms were minimal. One patient who was admitted for herniorrhaphy was symptom-free but was given aluminoid as a prophylactic measure because of a long-standing ulcer history and the effect which an operative procedure frequently has in such cases. He was symptom-free on discharge. No follow-up has been possible in this case.

The response to hospital treatment of the 17 patients admitted with severe symptoms as shown by their condition at discharge was as follows:

One patient still had sufficient disturbance to be classified as severe, although she had made definite progress. Evaluation of this case was complicated by the presence of unrelated disease and marked psychogenic disturbance. She was discharged on aluminoid therapy.

One patient had moderate symptoms on discharge. Operation was advised and refused. He was discharged on tricalsate because of an exacerbation of symptoms on both forms of aluminum hydroxide.

Four patients were discharged with minimal symptoms, 2 on aluminoid therapy. One was discharged on amphojel therapy because of the relief he obtained from night pain, abdominal distention, and heartburn which had been persistent with aluminoid therapy. The other was discharged on tricalsate because it gave immediate relief from occasional distress which was not true of either of the forms of aluminum hydroxide.

Six patients were symptom-free at the time of discharge on aluminoid. Of the remaining 5 without symptoms, 3 patients were discharged on amphojel; 1 because he had no relief from symptoms on aluminoid therapy and complete relief with amphojel; 1 did as well on aluminoid as on amphojel, and the third had his medication changed because of severe distress which was thought to be

due to ulcer symptoms but which subsequently proved to be caused by unsuspected gallstones.

One patient was discharged on no antacid, since he remained symptom-free without medication. One was discharged on both amphojel and aluminoid.

The response of the 10 patients admitted with moderate symptoms was as follows:

One patient still had moderate symptoms on discharge although she was considered improved after her hospital stay. Operation was advised and refused. Two patients were discharged with minimal symptoms, one on aluminoid therapy and the other with aluminoid and tricalsate. In the latter case it was found that this combination kept the patient more comfortable than the use of either amphojel or cremalin alone. Seven patients were discharged symptom-free on aluminoid. Four patients admitted with minimal symptoms were discharged symptom-free on aluminoid.

Analysis of Symptoms of Patients Receiving Reactive Aluminum Hydroxide

Thirty-one patients received amphojel as the principal adjunct to the basic ulcer regimen while in the hospital. Of these, 18 were admitted with severe symptoms, 12 with moderate symptoms, and 1 with minimal symptoms.

The response to hospital treatment of the 18 patients admitted with severe symptoms was as follows:

One patient still had severe symptoms when he left the hospital. This patient subsequently had a subtotal resection. He was discharged on amphojel.

Two of three patients who had minimal symptoms at the end of the period of hospitalization were discharged on amphojel and the third did not require antacid therapy. Two of these 3 patients were difficult to manage because of lack of cooperation and psychogenic disturbances. The other patient refused an advised operation.

Fourteen patients were discharged symptom-free; 13 on amphojel and one on tricalsate, which gave more immediate relief from his occasional distress. The 12 patients who were admitted with moderate symptoms were all discharged symptom-free, 11 on amphojel and 1 on no antacid. The 1 patient admitted with minimal symptoms was symptom-free on discharge and was discharged on amphojel.

Table 3 is the summary of patients treated with nonreactive and reactive aluminum hydroxide.

Analysis of the Follow-up of the Patients Receiving Nonreactive Aluminum Hydroxide

No follow-up was obtained in 2 of the 17 patients who were admitted with severe symptoms. Six patients in this group were discharged on other medi-

cation. Of the 9 remaining, the follow-up ranged from one to ten months, with an average of five months.

One of these still had severe symptoms. This case has been commented upon previously. Two patients had minimal symptoms and 6 patients were symptom-free.

TABLE 3
Comparison of Symptoms at Time of Discharge from the Hospital

A. In patients with severe symptoms on admission

ALUMINOID (17 CASES)		AMPHOJEL (18 CASES)	
Symptoms	No. of patients	Symptoms	No. of patients
Severe*	1	Severe	1
Moderate	1	Moderate	0
Minimal	4	Minimal	3
Absent	11	Absent	14

B. In patients with moderate symptoms on admission

ALUMINOID (10 CASES)		AMPHOJEL (12 CASES)	
Symptoms	No. of patients	Symptoms	No. of patients
Severe	0	Severe	0
Moderate	1	Moderate	0
Minimal	2	Minimal	0
Absent	7	Absent	12

C. In patients with minimal symptoms on admission

ALUMINOID (4 CASES)		AMPHOJEL (1 CASE)	
Symptoms	No. of patients	Symptoms	No. of patients
Severe	0	Severe	0
Moderate	0	Moderate	0
Minimal	0	Minimal	0
Absent	4	Absent	1

* This patient's symptoms were difficult to evaluate because of unrelated disease.

Of the 10 patients who had moderate symptoms on admission to the hospital, no follow-up was obtained in 1 case. The follow-up in the 9 remaining cases varied from one to eleven months, with an average of four months. Because of nausea and anorexia, the treatment in 1 case had been changed to amphotojel four months after the patient left the hospital, with complete relief of symptoms. Another had resumed the use of amphotojel of her own volition six months after leaving the hospital because she got better relief from symptoms, although during her hospital stay she obtained adequate relief of symptoms and was much less constipated on aluminoid therapy. Of the 7 patients remaining, 1 had moderate symptoms, 3 minimal symptoms, and 3 were symptom-free.

The 4 patients who had minimal symptoms on admission to the hospital were symptom-free after an average follow-up of six and one half months. All were still taking aluminoid.

Analysis of the Follow-up of Patients Receiving Reactive Aluminum Hydroxide

No follow-up was obtained in 1 of the 18 patients who were admitted to the hospital with severe symptoms. One patient was discharged from the hospital on no antacid, and 1 was discharged on tricalsate. Of the 15 remaining patients, a follow-up varying from one to nine months with an average of four months was obtained.

TABLE 4

Correlation of Acidity and Symptoms in 9 Patients with Follow-up in the Aluminoid Group

CASE	ADMISSION		DISCHARGE		FOLLOW-UP		DURATION
	Acid	Symptoms	Acid	Symptoms	Acid	Symptoms	
							<i>months</i>
29	High	Severe	Low	Absent	High	Minimal	10
4	High	Severe	Low	Absent	High	Absent	8
23	High	Moderate	Low	Absent	Low	Absent	11
6	High	Moderate	Low	Absent	Low	Minimal	7
20	High	Minimal	Low	Absent	Low	Absent	10
28	Medium	Moderate	Low	Absent	Medium	Minimal	2
32	Medium	Moderate	High	Moderate	Medium	Minimal	8
31	Medium	Severe	Low	Severe	Low	Severe	3
13	Low	Severe	Low	Absent	Medium	Minimal	9

One patient still had severe symptoms. He subsequently had a gastric resection. One had moderate symptoms, 3 had minimal symptoms and 10 patients were symptom-free.

Of the 12 patients who had moderate symptoms on admission to the hospital no follow-up was obtained in 3 cases. One patient had been discharged without antacid. Of the 8 remaining cases, 4 had minimal symptoms and 4 had no symptoms after a follow-up ranging from one to nine months, with an average of four months.

The 1 patient who had minimal symptoms on admission to the hospital was found to have minimal symptoms six months after discharge from the hospital.

STUDIES OF GASTRIC ACIDITY

In reporting gastric acidity we have used the term "low" to designate a range of free acid from 0 to 24 units, inclusive; "medium" for a range from 25 to 49 units, inclusive, and "high" for 50 units or more.

Gastric Analyses of Patients Receiving Nonreactive Aluminum Hydroxide

Twenty-six of the 32 patients who received aluminoid therapy had routine determinations of gastric acidity made near the beginning and end of their hospital stay. Of these, the acid on admission was high in 11 cases, medium in 10 cases and low in 5 cases.

TABLE 5
Comparison of Gastric Acidity at Time of Discharge from the Hospital

A. In patients with high acid on admission

ALUMINOID (7 CASES)		AMPHOJEL (1 CASE)	
Acidity	No. of patients	Acidity	No. of patients
High.....	0	High.....	0
Medium.....	1	Medium.....	0
Low.....	6	Low.....	1

B. In patients with medium acid on admission

ALUMINOID (8 CASES)		AMPHOJEL (8 CASES)	
Acidity	No. of patients	Acidity	No. of patients
High.....	2	High.....	2
Medium.....	0	Medium.....	1
Low.....	6	Low.....	5

C. In patients with low acid on admission

ALUMINOID (3 CASES)		AMPHOJEL (6 CASES)	
Acidity	No. of patients	Acidity	No. of patients
High.....	0	High.....	1
Medium.....	0	Medium.....	5
Low.....	3	Low.....	0

Four patients who had high gastric acidity on admission were given other ulcer therapy before discharge. Of the remaining 7, 6 had low acid and 1 had medium acid at the time of discharge. Eight of the 10 patients with acids in the medium range on admission were discharged on aluminoid. Two had high acids, and 6 had low acids. Three patients of the 5 with low acid on admission were discharged on aluminoid, all with low acid.

In the group of patients receiving nonreactive aluminum hydroxide therapy, 9 had determinations of gastric acidity made from nine to eleven months following discharge from the hospital. The results of these determinations are tabulated in table 4.

Gastric Analyses of Patients Receiving Reactive Aluminum Hydroxide

Seventeen of the 31 patients in the group receiving amphojel therapy had determinations of gastric acidity made near the beginning and end of their hospital stay. Of these, the acid was high in 1 case, medium in 9 cases, and low in 7 cases on admission. The one patient who had high gastric acidity on admission had low acid when he was discharged on amphojel.

One patient who had a medium gastric acidity on admission was discharged on another antacid. Of the 8 discharged on amphojel, 2 had high, 1 had medium and 5 had low acid values.

TABLE 6

Correlation of Acidity and Symptoms in 9 Patients with Follow-up in the Amphojel Group

CASE	ADMISSION		DISCHARGE		FOLLOW-UP		DURATION
	Acid	Symptoms	Acid	Symptoms	Acid	Symptoms	
							<i>months</i>
7	High	Moderate	Low	Absent	Low	Minimal	6
6	Medium	Severe	Low	Absent	Medium	Absent	5
16	Medium	Severe	Low	Absent	Medium	Moderate	2
23	Medium	Severe	Medium	Minimal	Low	Absent	1
32	Medium	Moderate	High	Absent	Medium	Absent	7
33	Low	Severe	Low	Absent	Medium	Absent	9
15	Low	Severe	Low	Absent	Medium	Absent	6
27	Low	Moderate	Low	Absent	Medium	Absent	2
5	Low	Minimal	Low	Absent	Medium	Minimal	6

One of the 7 patients who had low gastric acid on admission was discharged on no antacid. Of the 6 discharged on amphojel, 1 had high gastric acid and 5 had medium acid at the time of discharge.

A comparison of the two groups is tabulated in table 5.

In the group of patients receiving reactive aluminum hydroxide therapy, 9 had determinations of gastric acidity made from one to nine months following discharge from the hospital. The results of these determinations are listed in table 6.

SUMMARY

Thirty-two patients who were hospitalized for treatment of peptic ulcer were treated with a basic hospital regimen and nonreactive aluminum hydroxide. A control group of 31 patients was treated with a basic hospital regimen and reactive aluminum hydroxide. A comparison is made with respect to the clinical course and determination of gastric acidity of the two groups while in the hospital and during a follow-up period varying from one to eleven months.

In this study, the nonreactive form of aluminum hydroxide afforded no greater clinical improvement than did the reactive form.

No constant effect was noted on gastric acidity with either form of aluminum hydroxide, nor was any correlation observed between the severity of symptoms and the degree of gastric acidity.

The outstanding advantages of the nonreactive over the reactive form are the ease with which it may be carried about by ambulatory patients, the lack of any taste and the decreased incidence of nausea and constipation in patients receiving this medication.

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COMPLICATIONS FOLLOWING WAR WOUNDS OF THE ABDOMEN

MONROE A. McIVER, M.D.

Cooperstown, N. Y.

INTRODUCTION

The following report on complications arising in connection with abdominal wounds is based on observations made while serving with the 33rd General Hospital in North Africa and Italy.¹ The great majority of the patients had received their initial treatment in forward installations and had completed the most acute phase of their convalescence before admission to the 33rd General Hospital; in a few instances they were admitted immediately following injury. Those received from forward units arrived in surprisingly good condition considering the seriousness and multiplicity of their injuries, bearing witness to the excellent surgical care they had received. Nevertheless, an abdominal wound is always a grave hazard and many of the patients were still seriously ill on arrival. The wide range of complications which arose—various types of intraperitoneal infection, intestinal obstructions, and altered physiology and malnutrition resulting from intestinal fistulae, intestinal resections and so forth—created many problems in management and made the group an interesting one to work with.

GENERAL CONSIDERATIONS

The 284 cases of abdominal wounds discussed in this paper fall into three main groups (Table I): wounds of the gastrointestinal tract, wounds of the liver or spleen, and wounds where abdominal exploration revealed no significant visceral injury. The location of the injury in the 167 patients with gastrointestinal wounds is shown in Table II.

In the majority of cases the gravity of the situation was aggravated by the fact that the patient suffered *other injuries* as well as abdominal wounds (Table III). Compound fractures of the extremities, for example, necessitated the management of abdominal cases in casts or in traction; injuries of the spine or paravertebral nerves presented special problems which were primarily neurosurgical; osteomyelitis not infrequently occurred in connection with fractures of the pelvis; injuries of the genito-urinary tract often resulted in fistulae, requiring the assistance of the urologist; empyema or subphrenic abscesses frequently occurred in connection with thoraco-abdominal wounds.

¹The writer wishes to extend his thanks to the surgeons who permitted him to see and follow the abdominal cases under their care. Special thanks are due in this respect to Dr. Eldridge H. Campbell, Jr., Dr. Henry H. Hun and Dr. Arthur H. Stein.

Therapy consisted for the most part in general nursing care and restoration of the nutritional balance, in the re-establishment of the continuity of the gastrointestinal tract where indicated, by closure of fistulae or colostomies,

TABLE I
General Classification

Injuries to gastro-intestinal tract.....	167
Injuries to liver or spleen alone.....	51
Liver alone.....	42
Spleen alone.....	9
No significant visceral injury found on abdominal exploration.....	66
 Total number of cases studied.....	 284

TABLE II
Distribution of Wounds of the Gastro-intestinal Tract

Stomach		
Stomach alone.....	5	
Combined with injury to small intestine or colon.....	3	
Combined with injury to liver or spleen.....	10	18
Small intestine		
Small intestine alone.....	33	
Combined with injury to stomach.....	2	
Combined with injury to liver or spleen.....	7	42
Colon and small intestine		
Colon and small intestine alone.....	45	
Combined with injury to liver or spleen.....	5	50
Colon or rectum		
Colon or rectum alone.....	55	
Combined with injury to stomach.....	1	
Combined with injury to liver.....	4	60
		170
Less number of cases counted twice.....		3
Total		167

and in the treatment of complications. Restoration of the nutritional balance was an important task, since many of the patients were severely depleted; they had often been undernourished and exhausted at the time the wounds were received, and the initial operation together with postoperative dietary

restrictions further increased the deficit. Secondary anemia was common and was corrected by transfusions.

COMPLICATIONS

The greatest problem presented by these patients was the diagnosis and management of complications. The incidence of complications was high

TABLE III
Other Injuries Encountered in Patients with Abdominal Wounds

Wounds of extremities (often including compound fractures).....	87
Injuries to spine or paravertebral nerves.....	11
Fractures of pelvis (compound, comminuted).....	25
ilium.....	12
ischium.....	8
pubis.....	5
Wounds of the genito-urinary system.....	42
bladder.....	13
kidneys.....	22
ureter.....	2
urethra.....	5
Thoraco-abdominal wounds.....	58
Miscellaneous injuries (including injuries to larynx, eye, inferior vena cava, iliac vein, femoral artery and vein, pancreas, skull)	14

TABLE IV
Number of Patients That Developed Complications
(Note: 21 patients had multiple complications)

	NO. OF CASES STUDIED	COMPLICATIONS			
		No. of cases	Severe	Mod.	Mild
Injuries					
Gastro-intestinal tract.....	167	50	31	12	7
Liver or spleen.....	51	12*	11	0	1
Negative explorations.....	66	9	4	4	1
Total.....	284	71	46	16	9

* Ten were thoraco-abdominal cases.

(Table IV) and in many instances more than one complication occurred. It will be noted that of a total of 284 patients studied, 71 developed complications; these were classified as severe in 46 cases, moderate in 16, and mild in 9. The great majority occurred in patients having wounds of the gastrointestinal tract; here, out of a total of 167 patients, 50 developed complications. Twenty-one patients had more than one complication, for the most part severe and associated with gastrointestinal wounds. Among the 51 patients with wounds

of the liver or spleen, there were complications in 12 instances; but of these 10 were in patients with a chest wound as well, and the complication was related to that injury rather than to the abdominal wound. Where wounds of the liver or spleen were not associated with other injuries, convalescence was in general uneventful. Among the 66 cases where the abdomen was explored with negative results, complications occurred in nine. In eight, the complication was due to a wound of some extra-abdominal region or system, usually of the chest or the genito-urinary system, while in the one remaining case there is no reason to suppose that the laparotomy was in any way responsible for the complication that occurred during convalescence.

Though the incidence of complications in patients with abdominal wounds was high, it was my impression—without statistical proof—that during the two years in which I followed these cases the number of complications became less. I believe that this reflected the increased experience and skill in planning and in executing the initial operations and also the widescale introduction of penicillin.

Types of Complications

The types of complications and the frequency of their occurrence are shown in Table V. It will be noted that while the list is long and varied, infection was the factor directly or indirectly responsible for most of the complications. *Localized infections* made up the largest group, 41 in number. Infection of laparotomy wounds or an abscess of the abdominal wall developed in 14 instances. These infections were of varying degrees of severity but surprisingly enough there was no instance of complete disruption of the wound. In 10 cases a subdiaphragmatic abscess occurred, the wound being thoraco-abdominal in five of these. The abscess was located in the pelvis in seven instances; in other parts of the abdominal cavity in three. Pelvic abscess often developed insidiously, being diagnosed and operated upon during the second or third week following injury. At times they developed more rapidly, and in several instances the time interval was much longer. The development of these abscesses was usually accompanied by abdominal pain, fever, and an increase in the leucocyte count. In the long drawn-out, chronic infections the temperature was often only slightly elevated, and a rise in the white blood count at times gave a better indication of a collection of pus than was furnished by the temperature chart. Manifestations of functional obstruction—vomiting, distention and obstipation—often occurred in connection with the intraperitoneal abscesses. If there was any reason to suspect that an abscess might develop, frequent digital rectal examination was carried out, to detect and collection of pus in the pelvis, and the subphrenic region was carefully watched. Treatment consisted of drainage where indicated, subdiaphragmatic abscesses

being drained extraperitoneally where possible, pelvic abscesses quite frequently through the rectum with satisfactory results. In connection with fractures of the pelvis, in cases where the bullet had passed through the colon before entering the bone, a serious type of osteomyelitis sometimes occurred, resulting from contamination of the bone with the colon group of organisms.

Intestinal obstructions constituted an important and serious group of complications. Obstructive symptoms were not uncommon and constant alertness was required in order that the condition might be recognised early. There

TABLE V
Types of Complications

Localized infections.....	41
Subdiaphragmatic or subhepatic abscess.....	11
Pelvic abscess (including 1 with subcutaneous emphysema of leg and thigh).....	7
Retroperitoneal abscess.....	2
Infection of laparotomy wound or abscess of abdominal wall.....	14
Infection of wound about rectum (including 2 coccygectomies).....	3
Osteomyelitis of the ilium.....	4
Intestinal obstructions.....	15
Acute obstructions (one due to Meckel's diverticulum).....	7
Sub-acute obstructions.....	8
Fistulae.....	14
Gastro-intestinal: 3 small intestine; 1 large intestine; 2 rectum.....	6
Biliary, 3; biliary and urinary, 2; urinary, 3.....	8
Pulmonary.....	14
Embolism (fatal), 1; pneumonia, 5.....	6
Empyema or organized hemothorax (all thoraco-abdominal wounds).....	8
Miscellaneous.....	17
Infectious jaundice, 3; thrombo-phlebitis, 2; severe secondary hemorrhage, 2; severe malnutrition, 2; 1 each, hydronephrosis of kidney, pyelonephrosis, acute ventricular failure (recovered), meningitis, kidney stone, cystitis and bladder stone, neuritis, and acute psychosis.....	

were seven cases in which the obstruction was acute and severe and demanded immediate operation. These acute obstructions occurred, in general, a number of weeks after injury, when the adhesions were well organized, and consisted for the most part in kinking or torsion of the intestine or in herniation of the gut through a ring-like opening formed by adhesions. In one patient, although there were many adhesions due to the abdominal wound, the obstruction was really caused by a long Meckel's diverticulum adherent to the base of the bladder and showing early gangrene. The question as to whether or not a strangulation exists is sometimes a difficult one; in general, a fulminat-

ing attack with the peristaltic type of pain and an increase in the leucocyte count indicates the need for immediate operation. Operative procedures consisted of lysis of adhesions and reduction of the obstruction. No intestinal resections were required, for while in most cases there was some element of strangulation, the circulation was not severely jeopardized. All of the patients recovered.

Eight patients showed signs and symptoms of subacute obstruction, appearing relatively early after injury, often in association with intraperitoneal abscesses. Presumably in these cases there was a functional element due to the atony accompanying peritonitis, as well as light fibrinous adhesions. The patients were treated successfully with the Miller-Abbott tube. There were also five patients who at some time during their convalescence developed mild obstructive symptoms which responded to simple measures. These cases are mentioned here for the sake of completeness, but since the trouble was slight and the diagnosis not always clear, they are not included in Table V.

Patients who showed a tendency toward recurrent attacks of obstructive symptoms were given mineral oil twice a day by mouth, and this treatment seemed beneficial in alleviating mild symptoms and warding off an acute attack. The use of the oil was continued for a considerable period after the symptoms had subsided.

Fourteen patients developed *fistulae*, six of the gastrointestinal tract and eight of the biliary or urinary system. Two patients had high intestinal fistulae following intestinal resection and the formation of a double-barrel jejunostomy, and presented difficult and serious problems in management. Both showed an extreme degree of malnutrition and dehydration at the time of admission, and there was extensive digestion of the abdominal wall and separation of the wound edges. Such fistulae constitute a particularly serious hazard, and unless the patient is in desperate condition at the time of the initial operation, immediate anastomosis should follow resection.

The fistulae of the urinary or biliary system, or combinations of the two, did not in general prove very serious complications. The great majority healed spontaneously.

Pulmonary complications developed in 14 cases. In one instance there was a fatal embolism; pneumonia, for the most part mild and responding promptly to chemotherapy, occurred in five instances; there were eight cases of empyema or organized hemothorax, all in patients with thoraco-abdominal wounds.

The *miscellaneous complications* included three cases of infectious jaundice. The disease was mild and was important only because its occurrence in patients with abdominal wounds raised interesting points in differential diagnosis. Thrombophlebitis of the veins of the extremities occurred only twice, which was somewhat surprising and was probably accounted for on the basis of the

youth of the patients. There were two cases of severe secondary hemorrhage, —one from a wound of a branch of the internal iliac artery (treated by ligation of the main trunk of this artery), the second from an injury of the deep epigastric artery. The two cases of severe malnutrition were associated in both instances with high intestinal fistulae.

MORTALITY

In the total series there were six deaths (Table VI). Three of these patients entered the Hospital in shock, shortly after injury, and died within 24 hours. Among those who survived the early period after injury there were only three deaths. One occurred in a patient with a high intestinal fistula who developed a number of other complications. The second was in a patient who suffered

TABLE VI

Mortality

TOTAL NO. OF CASES	TOTAL NO. OF DEATHS	LOCATION OF INJURIES IN FATAL CASES	CAUSE OF DEATH
284	6	Colon and small intestine	Shock
		Colon; also spleen, kidney, lung	Shock
		Liver	Rupture of liver
		Colon and small intestine	Malnutrition, fistula of small intestine; pyelonephritis; urinary fistula; intraperitoneal abscess
		Colon and small intestine, also spleen and spine	Meningitis
		Rectum	Pulmonary embolism

from multiple complications and died of meningitis; it was found at autopsy that there had been a direct spread of infection from a retroperitoneal abscess along the track of the missile into the spinal canal. The third death was caused by a pulmonary embolism following a wound of the rectum.

It is interesting that although there are probably no patients with war wounds who are subject to more frequent or graver complications than those with wounds of the abdomen, the number of deaths in this series was so low. This fact must be attributed in large part to the sound surgery that was carried out at the forward installations and to the fact that the patients were young, hardy soldiers. Their recuperative powers are remarkable; and in no case, regardless of the number of setbacks which may develop, should there be any relaxation in the therapeutic endeavors. The outcome is frequently gratifying in cases which seem hopeless.

CONCLUSION

The picture given here of complications arising in connection with war wounds of the abdomen does not tell the whole story. It takes into account only those existing at the time the patient was admitted to the 33rd General Hospital or occurring while he was there, and makes no attempt to determine the incidence or evaluate the seriousness of complications of the early post-operative period that had been cleared up in forward installations, or of those that may have occurred in hospitals further to the rear. The complete picture would also include the complications which will undoubtedly appear sooner or later in many of these patients as sequelae to their abdominal wounds. The altered physiology caused by various operative procedures may well produce a wide variety of symptoms; and the adhesions resulting from the trauma of wound and operation, and in many instances from serious intra-peritoneal infections, will at times result in acute or subacute intestinal obstructions.

THE TREATMENT OF WAR WOUNDS INVOLVING THE GASTRO-INTESTINAL TRACT

ROBERT M. ZOLLINGER, M.D.

Department of Clinical Surgery, Ohio State University, Columbus, Ohio

INTRODUCTION

The seriousness of war wounds of the abdomen has long been appreciated. Such wounds are commonly associated with injury to the gastro-intestinal tract. In World War I, the mortality rate in such casualties exceeded 50 per cent (table 1). The management of these cases in World War II has reduced the mortality rate to 25 per cent or less. From two reported series of casualties totalling approximately 136,000, there were about 5,450 abdominal wounds, or an incidence of 4 per cent (1). While the overall mortality was 25 per cent or less, it more nearly approximated 35 per cent in that group of cases having multiple wounds of the gastro-intestinal tract, or thoraco-abdominal wounds.

These statistics do not give the true picture of all abdominal wounds, since they only include those patients admitted to medical installations. A large number of such men expired a short time after injury from exsanguination. This is especially true if one of the great vessels has been perforated (fig. 1). Those individuals who survive their wounds for a period of time frequently lose large amounts of blood as a result of damage to the small mesenteric vessels or associated injury to the liver, spleen, etc. Blood may escape free into the peritoneal cavity, be restricted between the layers of the mesentery, or escape into retroperitoneal tissues.

Emerson and Ebert (2), in their studies on shock in the forward areas, found the magnitude of the blood loss sustained by patients with abdominal wounds was substantially greater than had been generally realized. They made extensive laboratory determinations which demonstrated that the acute blood loss averaged 40 per cent of the expected normal blood volume in those patients having initial systolic pressures below 85 mm. of mercury. In every case, with this degree of hypotension, the diminution in volume exceeded 25 per cent. Since the surgeon hesitates to operate upon a patient with a systolic blood pressure under 100 mm. of mercury, it is significant to know that an average of 1250 cc. of blood and plasma was required to raise the systolic pressure in these patients from 85 mm. to 100 mm. of mercury or above. It was soon learned that the use of adequate amounts of whole blood was essential before, during, and after operation. While plasma was valuable in the far forward areas in the initial treatment of shock, it was inadequate preparation for those patients requiring a major surgical procedure.

Whole blood transfusions not only made it possible to operate on more of these patients but it gave the surgeon more time to do a thorough operative procedure. His first consideration was the control of active bleeding, followed

TABLE I
*War Wounds of Abdomen**

WAR	CASUALTIES	ABDOMINAL WOUNDS	INCIDENCE	MORTALITY
World War II	136,000	5,450	4%	21%
World War I				50+%

* Approximate figures

The mortality rate of abdominal wounds in World War II has been greatly reduced over World War I.

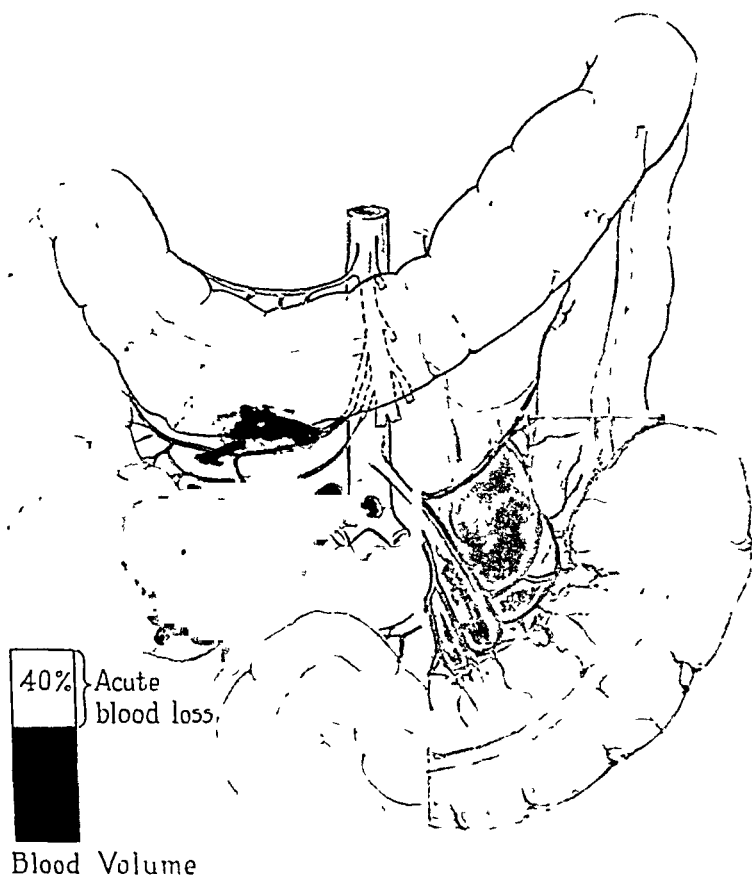


FIG. 1. WAR WOUNDS OF ABDOMEN

by a systematic exploration of the gastro-intestinal tract. Adequate blood transfusions insured a greater resistance on the part of the patients to combat the infection resulting from the inevitable contamination from perforation of the gastro-intestinal tract.

Emerson and Ebert (2) also found that it was not uncommon for some of these patients to lose as much as 2200 cc. of blood at the time of operation when they have extensive abdominal wounds. Widespread appreciation that these patients required large amounts of whole blood, combined with the fact that whole blood was available in the forward areas probably played the major role in the reduction of the mortality rate. Not only was the mortality rate lowered, but their convalescence was accelerated by repeated blood transfusions even in the late postoperative period.

OBSERVATIONS

While acute blood loss is responsible for early mortality in wounds of the gastro-intestinal tract, infection is accountable for a large percentage of the late mortality. It was soon learned that, regardless of the site of entrance of the missile into the body, a perforation of the gastro-intestinal tract had to be considered. This was especially true of those individuals having wounds of the buttocks, thighs, sacral or perineal areas. Perforations of the pelvic colon were not uncommon in such cases. The most minute perforation of the abdominal wall was suspected as a possible wound of entrance. Furthermore, a wound of entrance into the chest required a careful physical evaluation as well as a roentgenogram of the abdomen because of the frequency of combined thoraco-abdominal injuries. The availability of whole blood for repeated transfusions and the availability of well trained anesthetists made it possible for the surgeon to carry out a thorough examination of the entire gastro-intestinal tract at the time the abdomen was explored.

Perforations of the intestines were frequently multiple and many times difficult to locate. This was especially true in some wounds of the large intestine, because the perforation was momentarily sealed by hard feces or everted mucosa (fig. 2). Cases have been seen who were apparently recovering satisfactorily following closure of multiple wounds of the small intestine, who suddenly developed signs of peritoneal irritation. Secondary exploration demonstrated an overlooked perforation of the colon which apparently had been temporarily occluded.

In such seriously wounded individuals, the surgeon should do the simplest and safest technical procedure possible. Small wounds of the gastro intestinal tract were satisfactorily closed with purse string sutures (fig. 3). The results were better if relatively large wounds were closed, rather than attempting resection of the involved segment. Such wounds closed at right angles to the

long axis of the bowel did not result in obstruction. If the laceration was greater than one half the diameter of the bowel, or if there were multiple perforations with questionable viability of the blood supply, a resection was indicated. Exteriorization of the small intestine was contraindicated in war surgery because of the complicated and intensive care demanded by such cases.

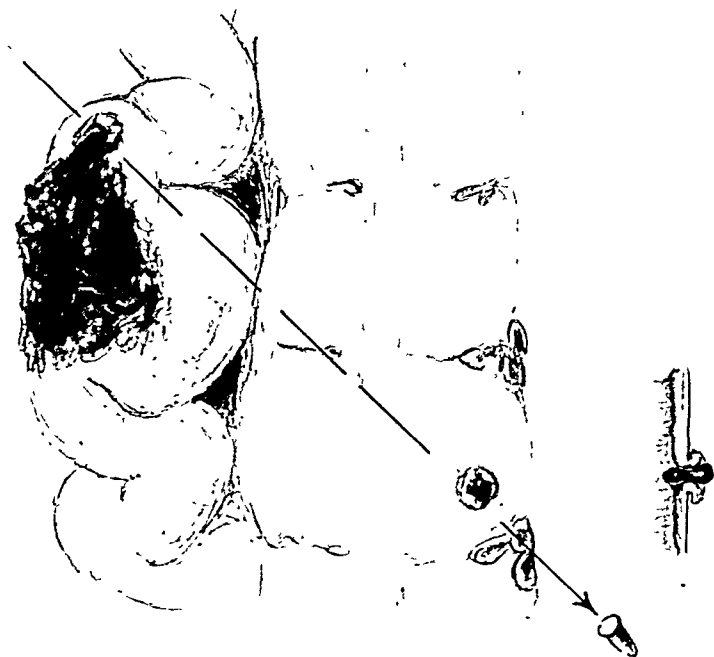


FIG. 2. WAR WOUNDS OF GASTRO INTESTINAL TRACT; VASCULAR DAMAGE
Large amounts of whole blood are required in the treatment of abdominal wounds

As the war progressed, it became apparent that the majority of patients who survived perforations of the colon had a colostomy as a part of their surgical treatment. It took time to convince the young surgeon that the construction of an artificial anus in a young man was not a reflection on the surgeon's technical ability and judgment, but was in reality a life-saving procedure. There was general acceptance of the surgical principle that a perforation of the colon should be exteriorized as the stoma of a colostomy (fig. 4). Also, if openings in the colon were closed, it was essential that the fecal stream be completely diverted by a proximal colostomy.

The loop type of colostomy was utilized with the perforation as the stoma

when it involved less than one half the diameter of the bowel. It was also used as a colostomy of choice proximal to the closure of multiple perforations (3).

The Mickulicz, or double-barrelled spur type of colostomy was commonly used for perforations larger than one half the diameter of the bowel, transection of the bowel, and injury requiring resection. The common errors in the per-

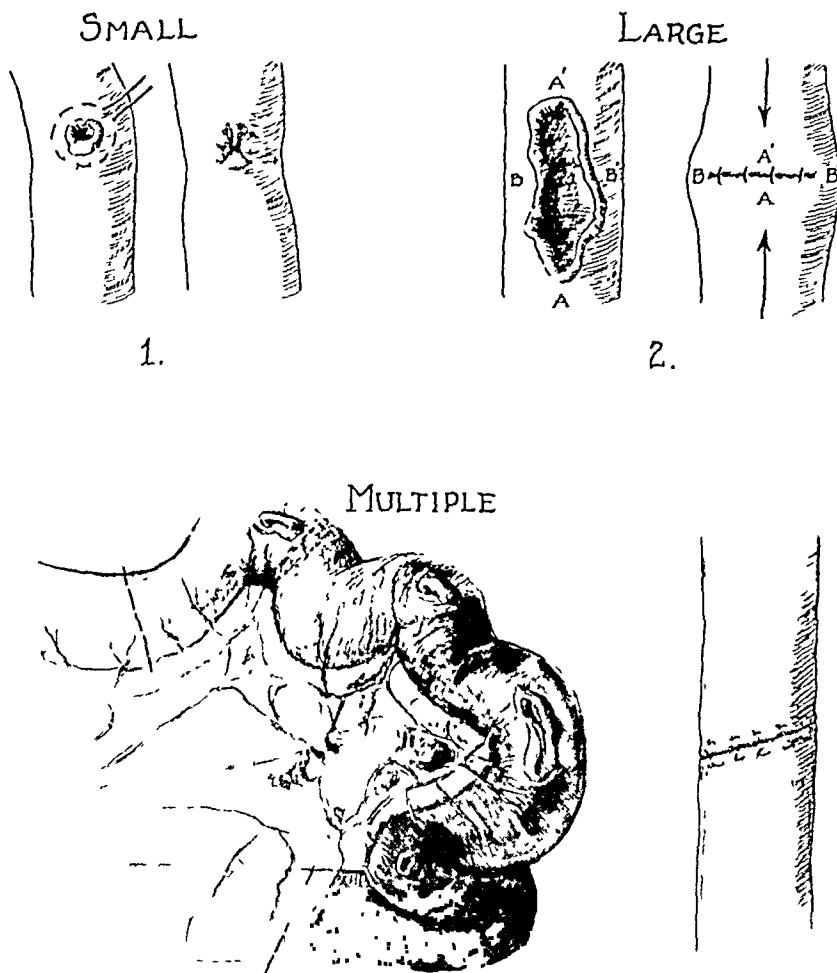


FIG. 3. WAR WOUNDS OF GASTRO INTESTINAL TRACT; BOWEL DAMAGE

Gross contamination commonly follows perforation of the small intestine. Perforations of the large intestine may be temporarily sealed by hard feces or everted mucosa.

formance of colostomy were largely due to the failure of the surgeon to adequately mobilize the bowel. It was occasionally not appreciated that extensive mobilization of the large bowel can easily be accomplished by division of its relatively avascular lateral peritoneal attachments. Colostomies performed under tension tended to retract to skin level or below, resulting in wound infections, wound disruptions, and in some instances peritonitis (4). The post-operative care, and the subsequent closure of the double-barrelled colostomy

were facilitated if the septum was five or six inches in depth. Furthermore, it was ascertained that it was possible to close successfully these colostomies within several weeks instead of waiting a prolonged period of time which is customary for colostomies performed in the treatment of malignant disease.

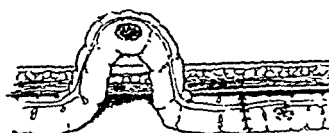
The role of chemotherapy in lowering the mortality rate of gastro-intestinal wounds is difficult to evaluate. The majority of these patients received vary-

I. SURGICAL PRINCIPLES

- a. Exteriorize perforation by colostomy.
- b. Primary closure of perforations;
proximal colostomy.

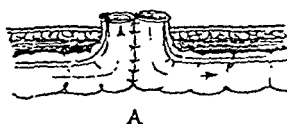
II. TYPES OF COLOSTOMY

a. Loop (indications)

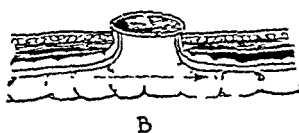


1. Perforation less than $\frac{1}{2}$ diameter of bowel.
2. Colostomy proximal to repaired perforations.

b. Spur (indications)



1. Perforations larger than $\frac{1}{2}$ diameter of bowel.
2. Injury requiring resection.



3. Transection of bowel.

FIG. 4. WAR WOUNDS OF GASTRO INTESTINAL TRACT; PERFORATIONS OF SMALL INTESTINE. Perforations of the small intestine should be closed by the simplest methods. Exteriorization of the small intestine is contraindicated in war wounds.

ing doses of the sulfonamides, in some instances locally, invariably parenterally (5). In certain theatres of operation, many were given 40,000 units of penicillin as soon as possible after being wounded, and the doses were continued during the early postoperative period.

Credit should certainly be given to the widespread usage of constant upper gastro-intestinal decompression by tube, and efforts to maintain fluid balance. Various types of rubber intubation tubes were made available to forward in-

stallations, and were generally utilized, although it was often necessary to improvise the mechanism for producing constant suction.

The patients with abdominal wounds were classified as non-transportable and given the highest of priority for early operation in the forward areas. Although many types of seriously wounded patients could be safely transported early after operation, it was soon found that this was harmful to the patient who had had surgery for gastro-intestinal injuries. Better results were obtained when they were retained as non-transportable for at least ten days following operation.

While the above factors are very important, it must not be forgotten that our Army was organized in such a manner that capable surgeons were available with the essential equipment and supplies to treat these cases in the far forward areas. Due credit should be given to the splendid work done by the medical officers in the Division areas as well as in the far forward hospitals. It should not be forgotten, however, that a great deal of surgery was necessary in the hospitals in the Zone of Communications as well as in the Zone of the Interior. It is probable that there was a late mortality of 5 to 10 per cent in those patients requiring subsequent surgical procedures.

A certain morbidity and mortality will continue in this group of patients from intestinal obstruction as a late result of their war injury. This group of patients will no doubt present variable gastro-intestinal complaints which will be a diagnostic challenge to many physicians in the future.

CONCLUSIONS

1. The mortality rate of abdominal wounds of World War II has been reduced to approximately 25 per cent. This is in contrast to a mortality rate of over 50 per cent in World War I.

2. Many factors have been responsible for lowering the mortality rate. They are: (a) The availability and use of large amounts of whole blood for transfusions. (b) The availability of qualified surgeons in forward areas. (c) Colostomies in all wounds of the large bowel; avoidance of small bowel enterostomies. (d) The use of constant gastric suction and maintenance of fluid balance. (e) The probable benefit of all types of chemotherapy.

3. Patients will be encountered in the years to come who present either classical symptoms of obstruction or bizarre gastro-intestinal symptoms directly related to their war wounds.

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PRIMARY MEGACOLON

JEROME M. SWARTS, M.D.

Department of Gastroenterology, The Lahey Clinic, Boston, Massachusetts

INTRODUCTION

Since the publication of Hirschsprung's paper (1) in 1888, the subject of megacolon has aroused much interest. During the ensuing fifty-seven years many similar cases have been reported. The accumulated literature has been reviewed (2, 3) several times and there has been much discussion concerning etiology and therapy. As the result of numerous experimental and pathologic studies (4, 5, 6), and of accrued clinical experience, some light has been thrown upon the problem which, however, is still far from being solved.

No attempt is made in the present study to include a discussion of etiology or pathologic physiology. We have endeavored to evaluate the efficacy of the therapy employed in 28 cases of primary megacolon which have been observed at the Lahey Clinic.

MATERIAL

All of the cases of megacolon seen at the Lahey Clinic from 1920 to 1946 were studied. Those cases were discarded in which obstructive lesions were found. Megacolon associated with idiopathic steatorrhea was not considered as an example of primary megacolon. Of course, no case of simple redundancy (dolichocolon) was included in this series.

We were able to collect 28 cases which satisfied our criteria for the diagnosis of primary megacolon. Of these, one case came under our observation late in 1945; since a second-stage colectomy is about to be performed at the time of this writing, no follow-up study is available.

Of the 28 cases in this series, 20 are of the congenital variety. Two cases were definitely acquired. The remaining 6 were indeterminate and may be either congenital or acquired.

There is an almost equal distribution of cases according to sex. In the entire primary group, the disease occurred in 13 male and in 15 female patients. Nine males and 11 females comprise the congenital group.

The youngest patient in the series was 21 months old and the oldest was 66 years of age when first seen. These 2 cases were classified as congenital and as indeterminate, respectively. The age distribution in the series is shown in table 1.

Seven patients, all having the congenital variety of megacolon, were submitted to operation. Colectomy was performed in 5 cases. Combined colectomy and sympathectomy was performed twice. Bilateral lumbar sympathectomy was performed upon 2 patients. The remaining 21 patients of the

series were managed medically; of these, 13 were considered as congenital types.

The only complication was that of volvulus. This occurred at some time during the courses of 3 patients.

Follow-up observations varied in length from two months to twenty years. The average length of time during which patients were followed was slightly less than four years.

SYMPTOMS AND SIGNS

Constipation, requiring the frequent use of laxatives and/or enemas, was by far the most common complaint of these patients. This was usually continuous, but in several cases was periodic. Some patients responded to enemas; others were completely refractory to enemas and laxatives. Abdominal

TABLE 1

AGE	ENTIRE PRIMARY GROUP	CONGENITAL	ACQUIRED	INDETERMINATE
<i>years</i>				
0-9	4	4		
10-19	12	11	1	
20-29	1	1		
30-39	5	4		1
40-49				
50-59	5		1	4
over 59	1			1
Total.....	28	20	2	6

pain was a common complaint. Several patients gave a history of, or were observed to have, episodes of acute intestinal obstruction. This was due to impaction or volvulus. Vomiting is not uncommon in these patients and is probably the result of pressure exerted upon the upper gastrointestinal tract. The development of fecal impactions requiring manual removal under spinal or general anesthesia was encountered several times. A history of diarrhea alternating with constipation was elicited in a number of cases. This is the diarrhea of overflow with the irritating effect of laxatives and enemas superimposed. Other rare symptoms were dysuria, dyspnea, excessive flatus and fatigue. Two patients gave a history of weight loss.

Abdominal signs were absent in approximately one-half of the cases at the time of the initial examination. Physical signs, when present, consisted of one or more of the following: abdominal distention, a palpable mass, and tenderness. Evidence of poor nutritional status was noted in 7 patients (table 2).

It is of interest to note that one patient whom we classified as having the

congenital variety of primary megacolon was found, at operation, to have a very large, dilated urinary bladder. The colon was of huge size and thick-walled.

RESULTS

We have evaluated our results as poor, fair, good, and excellent. Our criteria consisted of the absence of pain, discomfort, distention, and freedom from impactions. We believe that the aim of therapy should be the maintenance of a useful life, with a paucity of symptoms and little or no disability. Quantitative estimation and the employment of absolute criteria are of course impossible in a study of this kind. Whenever doubt existed as to the degree of improvement in a particular case, we tended to choose the lesser grade.

TABLE 2
Symptoms in Order of Decreasing Frequency

Constipation.....	26
Abdominal pain.....	18
Acute abdomen.....	8
Anorexia and nausea.....	8
Vomiting.....	6
Diarrhea.....	6
Fecal incontinence.....	3
Weight loss.....	2
Tenesmus.....	2
Excessive flatus.....	1
Dysuria.....	1
Dyspnea.....	1
Fatigue.....	1

This report is made with the complete realization that, because of the small size of the series, the results are not statistically significant.

In all, 28 patients have been treated. Medical management alone was employed in 21. The remaining 7 patients were treated by surgical measures which included colectomy, lumbar sympathectomy, or a combination of the two. On the basis of Hurst's (7) hypothesis of anal achalasia as the mechanism responsible for megacolon, pectenotomy and anal dilatation were performed several times, but without benefit.

The patient upon whom a total colectomy was performed with an excellent result fifteen months postoperatively had had five months of medical management, but finally became refractory to all conservative measures; hence, the decision in favor of surgical intervention. A second patient in this group did well on medical management for two years, so well, in fact, that the diagnosis of megacolon was questioned for a short period. Because the mother of the patient did not strictly maintain the outlined regimen, a sympathectomy

was performed. During the year after operation, it was necessary to remove fecal impactions twice under anesthesia. A third patient did well with the use of conservative measures, but it was thought that sympathectomy would obviate the necessity for careful bowel management. The patient improved temporarily for a period of two months, but then abdominal distress and obstipation developed. The remaining patients in the surgically treated group had had, for various reasons, no adequate preoperative trial of medical management. A summary of the results of surgical treatment is given in table 3.

TABLE 3

OPERATION	RESULT
Colectomy and ileosigmoidostomy.....	Excellent
Colectomy and ileosigmoidostomy.....	Died
Resection of the sigmoid and unilateral sympathectomy.....	Too early to evaluate
Colectomy, ileosigmoidostomy, and bilateral sympathectomy...	Poor
Resection of the sigmoid.....	Fair
Bilateral sympathectomy.....	Fair
Bilateral sympathectomy.....	Poor

TABLE 4

	ALL PRIMARY CASES	PRIMARY CONGENITAL
Excellent.....	6	4
Good.....	10	7
Fair.....	4	2
Poor.....	1	0
Total.....	21	13

Conservative measures were employed in 21 cases. Sixteen patients had good or excellent results. Thirteen of these cases were definitely of the congenital variety; again, good or better results were obtained in 11 cases. These are summarized in table 4.

It is evident that, in this series, the results of conservative treatment were better than those of surgical therapy. It must be realized, however, that some patients respond poorly to both surgical and medical management and that this must be taken into consideration in comparing the results of the two methods.

Roentgenographic improvement was noted in only 4 cases. The colon of one patient with the congenital variety of megacolon showed a restoration to normal size six years after medical treatment was begun. The roentgenograms of 2 patients, with indeterminate variety, revealed some diminution in the size of the colon at two months and at six years, respectively, after the

onset of treatment. The size of the colon in one case of acquired megacolon was significantly smaller after three years of conservative management. It is obvious that reduction in the caliber of the colon as demonstrated by the barium enema does not parallel clinical improvement. The failure to return to normal size is explained by the fibrosis and muscular hypertrophy that occur in longstanding cases (8).

DISCUSSION

That primary megacolon is a rare disease is evident when one considers that 28 cases have been seen at the Lahey Clinic in a period of twenty-five years. This is in accordance with the observations of other clinicians working in busy gastrointestinal and surgical clinics throughout the world (1, 2, 7, 8, 9, 10, 11).

Megacolon may occur at any age. At times it is difficult or impossible to determine whether the condition is congenital or acquired. The question as to whether the disease may exist in a clinically latent form and subsequently become overt is a moot one at present.

This disease like most others varies in severity and in response to various therapeutic measures. Hence, there is no single method of management applicable to all cases. While the ultimate objective should be cure, it seems best to attempt to maintain these patients in a state of minimal discomfort and disability. In this series there were no deaths attributable to the disease *per se*.

Conservative management should be undertaken first and should be carried on for at least one year before resorting to operative intervention. If volvulus or perforation should occur during this time, these complications should be treated appropriately by surgical means. In view of the fact that these complications are fairly uncommon, medical management with careful and frequent observations is entirely safe. Medical treatment should aim at keeping the colon as nearly empty as possible at all times. Dilatation and the formation of impactions are the result of the accumulation of feces over long periods of time and predispose to complications. Strict attention must be paid to the dietary habits of the patient; the diet must be of as low residue as possible, compatible with adequate nutrition and palatability. Liberal vitamin supplements should be used. Although a patient may defecate frequently with diets of higher residue, such diets are not only irritating, but also result in a cumulative increase of colonic contents over weeks, months and even years.

The regular use of enemas is a necessary part of medical management; these should be of mineral or of vegetable oils, and of physiologic saline solutions. At times small enemas of magnesium, glycerin, and water may be required for the removal of rectal impactions. Enemas should be prescribed

according to a schedule which will vary with the severity of the process; these may have to be given daily or several times a week. When treatment is begun, mechanical cleansing must be done often in an effort to rid the bowel of contents which may have been present for months or even longer. Although patients may seem apparently quite well for a short period after enemas are discontinued, the remission is usually short-lived, and impaction results. Laxatives are never indicated.

An adjuvant which seems to have a beneficial effect in certain cases is mecholyl bromide in doses of 0.1 to 0.2 gm. (10). We have employed this drug in a few cases, but its efficacy is difficult to evaluate. Antispasmodics may be necessary, for these patients do manifest spasm even in the presence of megacolon. Sedation should be given when indicated for anxiety and apprehension which result from the basic difficulty. Initial treatment is usually best carried out in the hospital.

If, after a period of one year, the patient continues to have a great deal of discomfort, develops frequent impactions and continues to be in a poor nutritional state or is markedly disabled, operative interference should be seriously considered. We do not believe that operation, except in the presence of complications, is ever justified for a patient under five years of age.

Our experience with sympathectomy has been discouraging. Others have reported good results but many of these have been temporary. The number of good results in several series has been extremely variable (2, 8). Interruption of nervous pathways for visceral pain by this procedure is undesirable, and so the operation is not entirely innocuous (12).

This leaves colectomy as the surgical procedure of choice. The surgical aspects of the problem have been reviewed by Whitehouse, Barger and Dixon (11), by Grimson, Vandergrift and Dratz (12), and most recently by Cattell and Colcock (13). Suffice it to say that the extent of resection is determined by the degree and extent of involvement. When wide resection is performed, an ileosigmoidostomy is necessary. Colectomy done in patients whose rectums are large and dilated gives poorer results than in those patients having rectums of normal caliber. These patients tend to have semiformal or liquid stools after operation, but still must be watched for impactions.

SUMMARY AND CONCLUSIONS

1. Twenty-eight cases of primary megacolon have been observed at the Lahey Clinic during the past twenty-five years. Of these, 20 were congenital, 2 were acquired, and 6 were indeterminate.

2. The only complication was that of volvulus which occurred in 3 cases.

3. Twenty-one cases were managed medically, 16 with good or excellent results. Seven patients were treated surgically by sympathectomy, colectomy,

or a combination of the two. There was only one excellent result in the surgically treated group.

4. Significant roentgenographic improvement was noted in only 4 cases. There is no correlation between clinical improvement and colonic size as demonstrated by the barium enema.

5. A medical regimen is outlined.

6. A trial of medical management should be maintained for one year and should be abandoned only because of marked disability and severe symptoms or because of supervening complications. No patient under five years of age should be treated surgically.

7. At present colectomy is the surgical procedure of choice. Sympathectomy is irrational and its efficacy does not justify its continued use.

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A SIMPLIFIED PROCEDURE FOR THE DETERMINATION OF PEPSIN AND TRYPSIN CONCENTRATIONS IN DIGESTIVE JUICES¹

M. H. F. FRIEDMAN

Dept. of Physiology, Jefferson Medical College

INTRODUCTION

Recently Riggs and Stadie (1) described a photoelectric method for the determination of the peptic activity of gastric juice. The same principle of turbidimetric measurement was adopted by us for determining the tryptic activity of pancreatic juice (3). Both procedures in our hands have yielded very satisfactory results. Determinations of pepsin and trypsin concentrations in color-free specimens of digestive juices can be made rapidly with a high degree of accuracy and with a minimum amount of preparatory work.

However, determinations on samples of gastric juice or duodenal contents containing more than traces of coloring matter, such as bile or blood, can be made only with difficulty. Furthermore samples of high and low peptic activity (or tryptic activity, as the case may be) cannot be compared readily without preliminary determination of the range in which these activities lie. In addition, the necessity for a photoelectric colorimeter prevents general use of the method in the clinic since many clinics have either no photoelectric instrument or only limited access to one. It therefore seemed desirable to modify the original procedures so as to overcome the above-mentioned limitations but without sacrificing the main advantages. In the method to be described peptic and tryptic activities are measured as the time taken for digestion of the substrate to proceed to a given end-point. The method is simple and inexpensive and has proved to be both accurate and rapid, and adaptable for routine examinations of gastric and duodenal contents in either the clinic or office laboratory.

MATERIALS

Substrate. A suspension of coagulated egg white is prepared as described by Riggs and Stadie. The white of a fresh egg which has been boiled for ten minutes is weighed and ground in a mortar. For each gram of egg white 5 ml. of distilled water is added and the suspension is passed through a hand homogenizer four or five times.² The volume of the suspension is doubled by the addition of distilled water and then is passed again through the homogenizer another four or five times. The albumen suspension is now centri-

¹ Aided by a grant from Wyeth Incorporated. The technical assistance of Miss I. H. Dougherty, B.Sc., is gratefully acknowledged.

² The Fisher hand homogenizer is a satisfactory apparatus for the purpose.

fused and enough distilled water is added to the supernatant material to make a total nitrogen content of 1.0 mg. per ml. This is usually achieved by dilution of the suspension with one-quarter volume of distilled water: we have found repeatedly that if the various steps in the homogenization and dilution process are kept constant the final dilution as described will contain approximately 1 mg. nitrogen per ml. A few thymol crystals are added as preservative. The stock suspension of albumen may be kept up to 4 months in a refrigerator without deterioration. The practically constant nitrogen content of the hen's egg white (4) makes duplication of the substrate a simple procedure.

Buffer. It is desirable that digestion should be carried out at a constant pH which is optimum for the enzyme on a particular substrate. For peptic digestion of egg albumen the optimum is about pH 1.2. While buffer solutions of this pH may be used, we have found satisfactory, and now prefer to use, a solution of 0.1 N hydrochloric acid. The relatively high proportion of acid substrate to gastric juice employed insures against change in pH even when samples of gastric juice from achlorhydric patients are used.

Determinations of trypsin concentration are carried out in a phosphate buffer of pH 7.8. This is prepared by adding 45.2 ml. of 0.2 N sodium hydroxide to 50 ml. of 0.2 M. acid potassium phosphate and diluting the whole to 200 ml. with distilled water.

Measuring tubes. A series of pyrex test tubes 15 mm. in diameter and 125 mm. high, are selected. Uniformity of internal diameter is tested simply by determining whether a given quantity of water, say 10 ml., reads the same height in each tube.

Water bath. The water bath is a glass-walled aquarium box 26 x 16 x 21 cm. equipped with thermostatic control.³ A portion of the bath at one end, 10 cm. in length, is kept clear of tube racks except for a narrow rack which can accommodate a single row of 4 tubes lining the wall of the bath (fig. 1). This portion of the bath serves as a viewing field. The remainder of the water bath is equipped with racks capable of holding the 15 mm. diameter pyrex tubes. The walls of the bath are painted black except for 10 square cm. of both the front and back walls in the area of the viewing field.

Lined glass plate. Five lines are ruled with black india ink on the ground surface of a fine grained ground glass plate 11 x 12 cm. (fig. 3). The distance between any two adjacent lines is 0.5 cm. The two outer lines are 3 mm. thick, the second two lines are 1.5 mm. thick and the middle line is 0.5 mm. thick. A thin coating of white petrolatum over the inked surface will protect the lines from rubbing off. The plate is inserted in a plate holder which is located in the viewing field exactly 2 cm. behind the front wall of the water bath (fig. 2).

³ Satisfactory results can be obtained by simply adding hot water as needed to an uncontrolled bath.

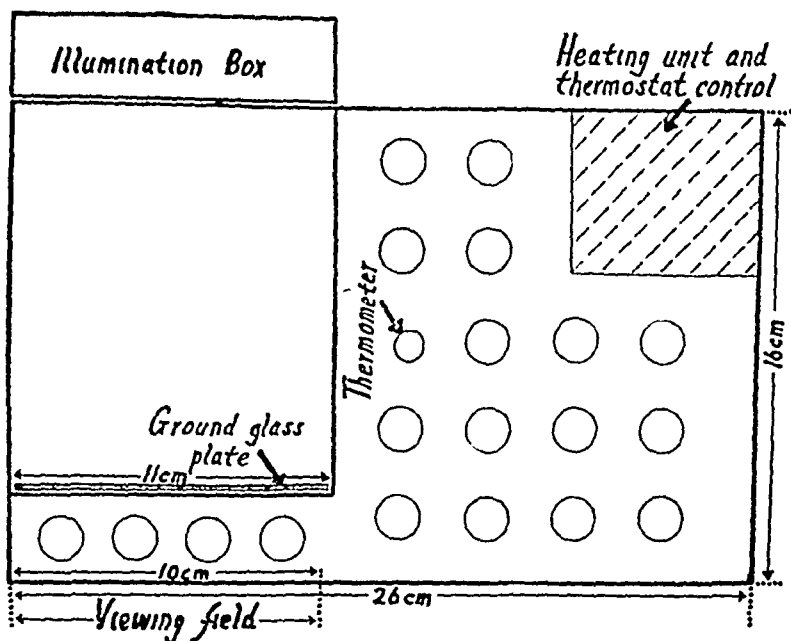


FIG. 1. WATER BATH, SURFACE VIEW, SHOWING POSITION OF ILLUMINATION BOX, AND GROUND GLASS PLATE IN THE VIEWING FIELD

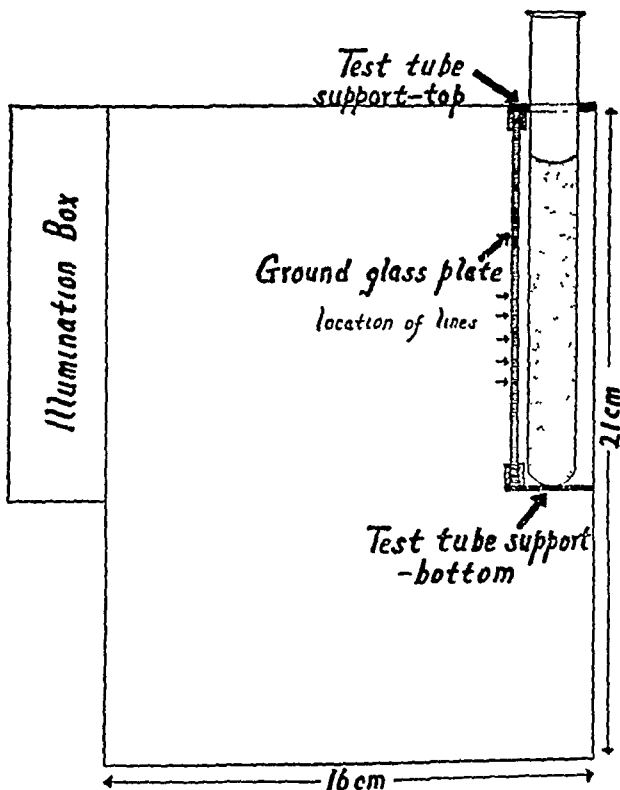


FIG. 2. WATER BATH, SIDE VIEW, SHOWING POSITION OF GROUND GLASS PLATE WITH INKED LINES

Illumination. It is necessary that the light be of standard intensity. A Kodak Safelight lamp No. 2, 50 watt, is used without its glass screen. The lamp is placed close against the back wall of the water bath so that the light forms a background to the whole viewing field (fig. 1). Without the lined ground glass screen, and with the water bath full, the light intensity in the viewing field should be 36 foot candles. With the glass screen in place the light intensity should be 26 foot candles.⁴

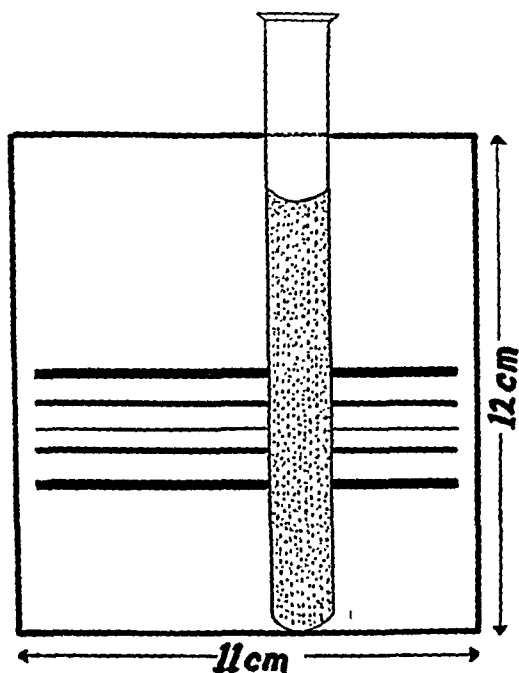


FIG. 3. LINED GROUND GLASS PLATE

PROCEDURE

Pepsin. Exactly 5 ml. of the substrate suspension is pipetted into a pyrex tube and kept in the water bath until the contents reach 38°C. This usually takes about 5 minutes. Into another pyrex tube are pipetted 0.5 ml. of the filtered juice and 4.5 ml. of 0.1 N HCl. This tube is also placed in the water bath for temperature equilibration. When the contents of both tubes have reached 38°C. they are mixed by rapidly pouring the contents back and forth three times and the tube containing the mixture is then placed in the viewing field of the water bath. The exact time of mixing is observed, preferably by

⁴ The intensity of the light reaching the viewing field may be measured simply by using a photographer's exposure meter with the exposed surface measuring 3.5 x 1 cm.

stopwatch. The tube is watched carefully for changes in opacity. As digestion proceeds the contents become less opaque and the ruled black lines can soon be seen through the mass. The broader outer lines become visible first and

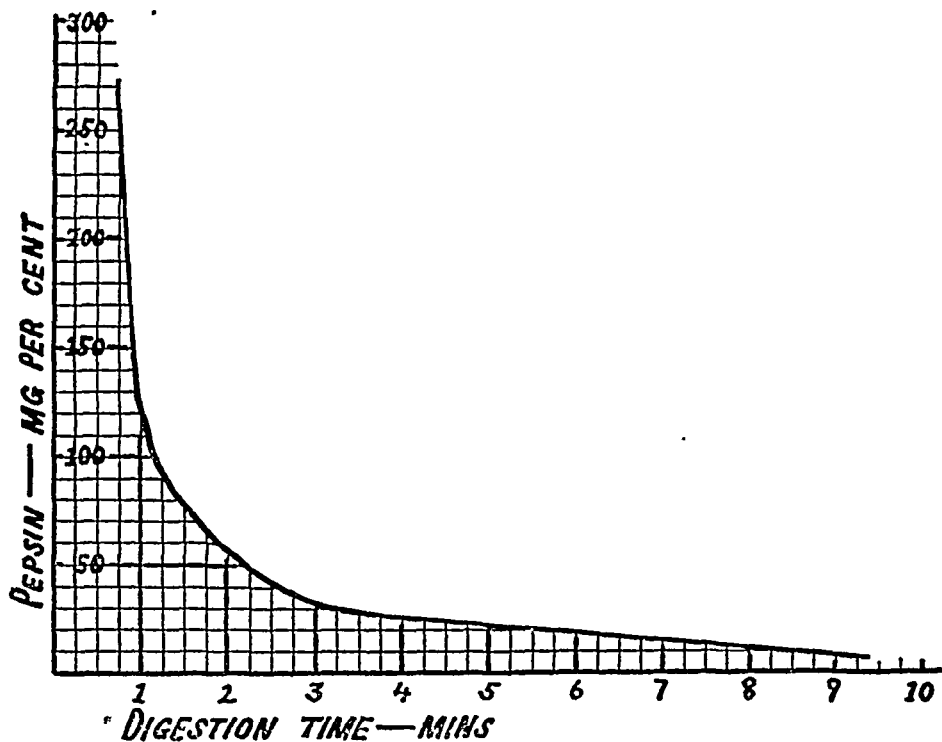


FIG. 4. CURVE SHOWING CORRELATION BETWEEN CONCENTRATION OF CRYSTALLINE PEPSIN AND TIME TO DIGEST SUBSTRATE

TABLE I
Human Gastric Juice

PATIENT	SEX	DIAGNOSIS	FASTING SECRETION			SECRETION 30 MIN. AFTER HISTAMINE		
			Digestion time		Pepsin <i>mg./100 ml.</i>	Digestion time		PePsin <i>mg./100 ml.</i>
			Minutes	Seconds		Minutes	Seconds	
D. K. P.	M	Trichiniasis	8	10	11	5	30	18
M. T.	F	Dermatitis	4	0	25	11	0	5
J. B.	M	Preparanoid psychosis	2	5	56	3	0	32
M. M. L.	M	Banti's syndrome	7	20	13	22	0	5
L. P.	M	Anacidity				35	0	5
S. N.	M	Duodenal ulcer	1	45	66	1	20	88
Secretion 30 min. after insulin								
M. W.	F	Duodenal ulcer	2	30	42	1	33	75
M. C.	M	Psychoneurosis	3	20	28		35	300
A. D. P.	F	Psychoneurosis	6	15	18		20	300

later the finer lines appear. The time when the fine single middle line becomes visible throughout the width of the tube is taken as the end-point.

Trypsin. Determinations are carried out in exactly the same manner as for pepsin, except that 1 ml. of the filtered duodenal contents is diluted with 4 ml. of the phosphate buffer pH 7.8.

TABLE II
Human Duodenal Contents

PATIENT	SEX	DIAGNOSIS	STIMULUS	TIME TO DIGEST SUBSTRATE			
				Fasting		20 min. after stimulus	
				Minutes	Seconds	Minutes	Seconds
A. D. P.	M	Arthritis	3 cc. ether instilled into intestine	30	0	4	45
D. C.	F	Postcholecystectomy syndrome	"	6	30	2	0
G. L.	M	Carcinoma of pancreas	"	No digestion		No digestion	
A. F.	M	Calcification of pancreas	"	" "		" "	
R. S.	M	Duodenal ulcer	Secretin	"	"	"	"
			"	14	10	3	45

TABLE III
Dog's Gastric and Pancreatic Juice

EXPERIMENTAL PROCEDURE	PEPSIN			TRYPSIN DIGESTION TIME	
	Digestion time		Mg/100 ml.		
	Minutes	Seconds		Minutes	Seconds
Gastric secretion from					
Pavlov pouch, one hour after meat meal.		25	300		
Main stomach, 30 minutes after histamine	1	10	100		
Vagotomized dog, 24 hours after meat meal (marked gastric retention).....	3	20	30		
Pancreatic secretion in response to					
Intestinal instillation of peptone.....					32
Intestinal instillation of HCl.....				1	20
Injection of secretin.....					55

CALCULATIONS

Pepsin. While the peptic activity of a given sample of gastric juice may be expressed in terms of the time taken to digest the standard amount of substrate to a standard end-point, it is more satisfactory to express activity in terms of the concentration of crystalline pepsin which will show a corresponding degree of activity. By substituting known concentrations of crystalline pepsin for the gastric juice, we constructed a digestion-time vs. pepsin

concentration curve (fig. 4), using the procedure outlined above. To facilitate reading and obviate the use of decimals, the concentration of pepsin is expressed as milligrams per 100 cc. The concentration of pepsin in a sample of gastric juice can be obtained by locating on the curve the point corresponding to the observed digestion time.

Trypsin. Because both commercial trypsin and crystalline trypsin contain a substance, presumably trypsin inhibitor (2), which interferes with digestion in higher concentrations, the construction of a digestion-time vs. trypsin concentration curve has been unsatisfactory. Furthermore, the concentration of active trypsin in these preparations varies widely. Consequently we have found it advisable to express tryptic activity in terms of the time taken by a given amount of pancreatic juice to digest the standard amount of substrate to a standard arbitrary end-point.

RESULTS

The peptic and tryptic activities of over one thousand samples of human and canine gastric juice, pancreatic juice and duodenal contents have been determined by the procedure described above. The relationship shown between digestion time and concentration of enzyme, as determined by serial dilutions of crystalline pepsin, is evidence that the procedure is reliable. In addition, using both gastric juice and pancreatic juice, we have found very good agreement between the results obtained by the method described herein and the photoelectric turbidimetric method (Riggs and Stadie, 1943; Friedman, 1947). Unless present in large amounts, bile or blood do not interfere appreciably with the reading of the end-point. However it should be remembered that bile and blood may have a direct inhibitory effect on the proteolytic action of the enzyme.

Tables I, II, and III show representative values for pepsin and trypsin concentrations respectively found in human and canine gastric juice, pancreatic juice and duodenal contents. They are given to illustrate the range of values which one may find by the method described.

SUMMARY

A relatively simple, rapid, and inexpensive method for accurate determinations of pepsin and trypsin concentrations in various digestive fluids is described.

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Section on
CLINICAL PATHOLOGICAL
CONFERENCES
and
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A. J. ATKINSON, Chicago, Ill.

H. M. POLLARD, Ann Arbor, Mich.
LEON SCHIFF, Cincinnati, Ohio

CLINICAL PATHOLOGICAL CONFERENCE

JOHN M. BERKMAN, M.D.
Division of Medicine

AND
ARCHIE H. BAGGENSTOSS, M.D.
Section on Pathologic Anatomy
Mayo Clinic, Rochester, Minnesota

PRESENTATION OF CASE

A man, sixty-eight years of age, came to the Mayo Clinic because of weakness and dyspnea and was hospitalized immediately. The only past history of any significance was of a severe attack of vomiting of blood and passage of tarry stools nineteen years previously. A short time after the gastrointestinal hemorrhage, a roentgenologic diagnosis of duodenal ulcer had been made. Prior to this attack the patient had had no digestive disturbances. Since the episode of bleeding he had had intermittent indigestion which was described as mild and was relieved by taking milk. With this exception he had been allegedly well until approximately four months prior to admission when he had noted that he was pale and weak and tired easily. This weakness and fatigue with some shortness of breath had gradually increased. Three months prior to admission severe acute sinusitis had developed. At that time erythrocytes had numbered 2,000,000 per cubic millimeter of blood and his physician had administered a form of reduced iron. However, this treatment had had little effect on the anemia. Two weeks prior to admission slight respiratory infection had developed and he had noted some abdominal distention. His temperature at that time had been 100°F. However, he had remained ambulatory and had continued to work until forty-eight hours before admission. The day before admission he had had rather marked dyspnea on any exertion and later in the day he had noted some dyspnea while at rest. On the day of admission he had been drowsy, although easily aroused, and weakness and shortness of breath had been bothersome. He had been nauseated for several days and had vomited once on the day of admission. He did not complain of pain.

On admission the patient weighed 167 pounds (75.7 kg.). His normal weight

was recorded as 170 pounds (77.1 kg.). He was pale and appeared weak and drowsy. The pupils reacted normally. The temperature and pulse and respiratory rates were within normal limits. The conjunctiva was thought to be slightly icteric. The tongue was moist and the nasopharynx dry. Some blood was found in the nose. A systolic murmur was heard over the entire precordium. There were frequent extrasystoles. Dullness was present at the bases of both lungs and moist râles were heard over the lower parts of the lungs. The abdomen was somewhat distended; however, no evidence of ascites was found. The liver which was smooth and not tender extended four fingerbreadths below the costal margin. The spleen was not palpable. No masses were palpable in the abdomen. The prostate was enlarged grade 1+ (grading is on the basis of 1 to 4 in which 1 represents the least and 4 the greatest enlargement) and no masses were found on rectal examination.

Urinalysis revealed that the specific gravity varied from 1.005 to 1.009 and albuminuria graded 2 to 3 (on a basis of 1 to 4) in all specimens. The test of urine for Bence Jones protein gave negative results. One urinalysis revealed a few granular casts. Usually erythrocytes were found in the urine, but erythruia was never graded more than 1. Pus, grade 1 (6 to 8 cells per high power field), was found in two specimens and the pH of the urine was 6. The values for hemoglobin varied from 5.6 to 8.1 gm. per 100 c.c. of blood; erythrocytes numbered from 1,810,000 to 2,480,000 per cubic millimeter and the leukocyte counts ranged from 3,900 to 7,500 per cubic millimeter. Results of serologic examination of the blood were negative. Roentgenographic examination of the thorax revealed cardiac enlargement and some congestion at the base of the right lung, and the roentgenologist was unable to exclude the diagnosis of bronchopneumonia. Examination of a special blood smear revealed some autohemagglutination. Regeneration was increased somewhat. The number of blood platelets, bleeding time and coagulation time were within normal limits. The values for blood urea varied from 264 to 320 mg. per 100 c.c. Concentration of chlorides varied from 578 to 587 mg. per 100 c.c. of plasma and the carbon dioxide combining power of plasma was 31.5 to 32.4 volumes per cent. The value for the serum protein was 8.6 mg. per 100 c.c. The prothrombin time was 21 seconds and the sedimentation rate was 152 mm. per hour (Westergren method).

During the first two days in the hospital the patient appeared to be fairly comfortable. On the following day difficulty in breathing increased. He appeared to be restless and later seemed to be confused. His drowsiness increased somewhat but he could be aroused to answer questions. Jerky movements of the arms and legs were noted. The blood pressure was 148 mm. of mercury systolic and 78 mm. diastolic. There was an increased amount of moisture in the lungs and respirations were noisy. He tolerated treatment by positive pressure with oxygen to the lungs rather well. He was not cyanotic before treatment with positive pressure was instituted; however, after a half hour of this treatment he became cyanotic. The noisy respirations had disappeared entirely. After forty minutes the treatment was discontinued and 100 per cent oxygen was administered by oxygen mask. The patient died four days after admission to the hospital.

DIFFERENTIAL DIAGNOSIS

Dr. Berkman: The patient obviously had had a gastro-intestinal hemorrhage nineteen years before admission to the hospital. This and his subsequent mild digestive disturbance which was relieved by ingestion of milk made it reasonable to assume that he had a duodenal ulcer. His downhill course apparently started three or four months prior to his admission. The course was characterized by pallor and progressive weakness which were symptomatic of the marked anemia revealed by the laboratory studies. The anemia was of the type which occurs with chronic renal insufficiency. In this case the uremia probably began rather insiduously and progressed until the patient was admitted to the hospital. The development of acute pulmonary edema and heart failure indicated the presence of long-standing and progressive cardiovascular and renal disease; this condition is characteristic of the late stages of chronic glomerulonephritis without edema. The albuminuria, low fixed specific gravity and retention of urea were also indicative of this condition. In the course of physical examination the blood pressure was found to be 148 mm. systolic and 78 mm. diastolic. It was suspected that this illness was a terminal one and that previously hypertension had been present.

It seemed that the concentration of plasma chlorides was of only negative significance. Carbon dioxide combining power of 32 and 31 volumes per cent is exactly what would be expected if acidosis were developing as the result of cardio-renal failure associated with uremia. The high sedimentation rate was consistent with the marked anemia, as well as with the terminal pneumonia which was suggested by the roentgenograms of the thorax. The enlargement of the liver was of some interest. It was interpreted as the result of congestion incident to the cardiac failure.

Two of the laboratory findings were significant. One was the autohemagglutination found on examination of the special blood smear. This finding immediately suggested the possibility of multiple myeloma, extensive malignant disease or overwhelming infection. The other significant laboratory finding was the value of the serum protein which, as mentioned previously, was 8.6 mg. Although this patient had been consistently losing protein through his urine, as evidenced by the albuminuria, grade 2 to 3, in several specimens of urine, the level of serum protein was elevated. It is of interest to note that the result of the test for Bence Jones protein was negative. Since this test is negative in about 40 per cent of cases of multiple myeloma it does not necessarily exclude this diagnosis. The finding of an elevated level of serum protein necessitated consideration of multiple myeloma, lymphosarcoma or extensive metastatic malignant disease. Although the lack of pain in the bones to some extent was evidence against a diagnosis of multiple myeloma,

it is known that approximately a fifth of patients who have multiple myeloma never complain of pain in bones.

Amyloid disease of the kidneys must be thought of in the presence of extensive albuminuria. Albuminuria and enlargement of the liver make the possibility of amyloidosis reasonable. A Congo red dye test which would have settled the matter was not carried out.

I might call attention to the fact that the patient was admitted to the hospital one evening and died the morning of the fourth day after that. Most of that time he was in serious condition. Also, the value for serum protein was not reported until after death had occurred. The patient unquestionably died of cardiac and renal failure with acute pulmonary edema. Uremia was obviously present and, while the entire picture was consistent with that of interstitial nephritis, it was quite apparent that this diagnosis was not adequate.

The clinical diagnoses were chronic glomerulonephritis without edema and duodenal ulcer.

To recapitulate, there were no evident changes in the peripheral vessels to suggest generalized arteriosclerosis.

Bleeding from a duodenal ulcer could not be definitely excluded because the condition of the patient made it impossible to obtain a stool for examination.

The concentration of protein of 8.6 mg. per 100 cc. of serum was a significant finding in this case and the presence of autohemagglutination in the special blood smear was consistent with this elevation in concentration.

PATHOLOGICAL DISCUSSION

Dr. Baggenstoss: At necropsy the heart was found to be enlarged and weighed 460 gm. as compared with an estimated normal weight of 300 gm. Bilateral hydrothorax (150 cc. of fluid in the right and 500 cc. in the left pleural cavity) and chronic passive congestion of the liver and the mucosa of the stomach and intestines were observed. An estimated 1,200 cc. of blood was present in the gastro-intestinal tract and this was considered to be the result of oozing from capillaries in the mucosa. Bronchopneumonia with organization was present in the upper lobe of the right lung. A stellate scar which was considered to be a healed ulcer was found on the posterior wall of the proximal portion of the duodenum. The kidneys were enlarged and finely granular. Their combined weight was 378 gm. as compared with an estimated normal weight of 300 gm. A few depressed scars, which measured up to 5 mm. in diameter were seen on the cortex.

On histologic examination, the most interesting changes were found in the kidneys. Most of the tubules contained eosinophilic hyalin and occasionally finely granular casts. Some of these casts were surrounded by phagocytes and occasionally by foreign body giant cells. An occasional cast appeared to

be calcified. A few of the tubules contained polymorphonuclear leukocytes. Degenerative changes were apparent in the lining cells of the tubules which were obstructed by casts. Many of the tubules were dilated. Focal collections of lymphocytes and an increase in connective tissue were observed in the interstitial tissue but the glomeruli were normal. The histologic appearance was typical of the so-called myeloma kidney. Hence sections of the sternal marrow were prepared and on examination were found to contain large numbers of plasma cells. These cells appeared to arise from numerous large reticulum cells in the marrow. These collections of reticulum and plasma cells had crowded out the cells of the normal marrow in many sites. Subsequent search led also to the finding of foci of plasma cells in the kidney and in the sinusoids of the liver and spleen.

The renal lesion in multiple myeloma has been classified as obstructive tubular disease by Bell. The tubular degeneration and atrophy are the result of obstruction of the tubules by large numbers of casts. Apparently the protein excreted in this disease forms very firm casts that lodge permanently in the tubules and provoke a foreign body reaction. Renal insufficiency results from obstruction of the tubules. According to Bell, who reviewed the literature in 1933, there has been only one case of proved renal insufficiency in multiple myeloma without Bence Jones proteinuria.

The final anatomic diagnoses in this case were as follows: multiple myeloma; obstructive tubular disease of kidneys (myeloma kidney) with uremia (clinical); mild interstitial nephritis (pyelonephritis); hypertrophy of the heart with congestive failure and gastro-intestinal hemorrhage; bronchopneumonia of upper lobe of right lung with organization, and healed duodenal ulcer.

CASE REPORT OF SUPPOSED RECURRENT PANCREATITIS

JULIAN M. RUFFIN, M.D.

PRESENTATION OF CASE

History. The patient, a 72 year old white married woman, reported to Duke Hospital on June 28, 1946, complaining of attacks of severe upper abdominal pain for the past six months. Her family, marital, and past histories were of no consequence. She had been entirely well until the onset of her present illness. Her attacks were characterized by the gradual onset of midepigastrie pain, radiating

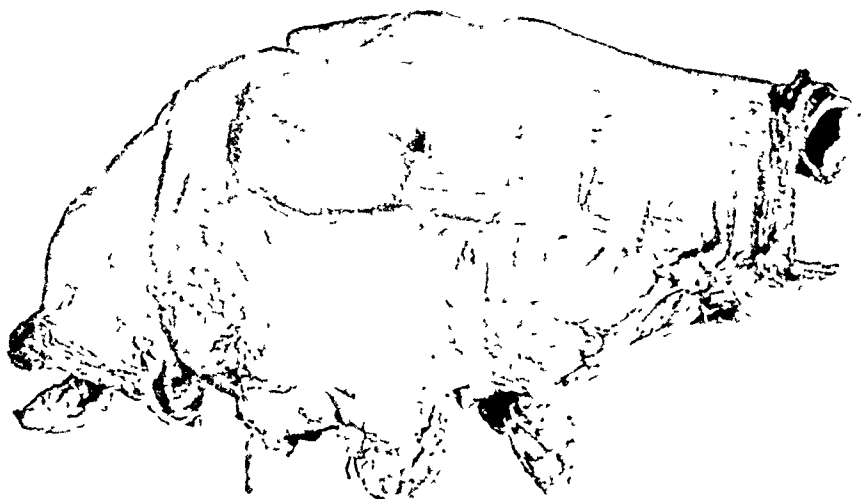


FIG. 1

to the left and to the back. The pain was constant, lasting several hours, and so severe as to require morphine for relief. This was accompanied by nausea and vomiting, but by no disturbance of bowel function and no jaundice. Following each attack she complained of generalized abdominal soreness, but in the interval she was entirely well. Her attacks occurred every three to four weeks and since the onset she had lost twenty-five pounds in weight. Two months before her abdomen had been explored in another hospital. Nothing abnormal was found and the gall bladder was drained. She continued to have her attacks.

Physical Examination. Examination revealed a well preserved, fairly well nourished white woman in no distress. Nothing of interest was noted, except for a mild hypertension (blood pressure 168/88). Nothing abnormal was felt in the abdomen.

Laboratory Studies. Urine, blood, and stool showed nothing of significance; the Van den Bergh was not elevated; a scout film of the abdomen was normal. No stones were observed. Gastrointestinal series and ileal studies showed nothing

definitely abnormal. With the diagnosis of chronic pancreatitis in mind a serum amylase test was run and the amount was found to be increased during an attack; the blood sugar was 180 mg/100 cc.; the urinary diastase normal.

Preoperative Diagnosis. Chronic, recurrent pancreatitis.

Operative Findings. At operation the pancreas, stomach, and duodenum were normal. There was a tumor in the terminal ileum. This was resected (Figures 1 and 2) and reported as a lymphosarcoma. She made an uneventful recovery.

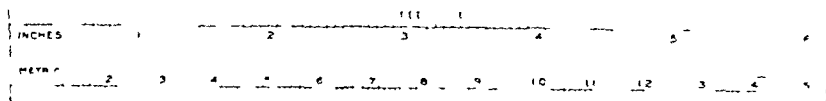
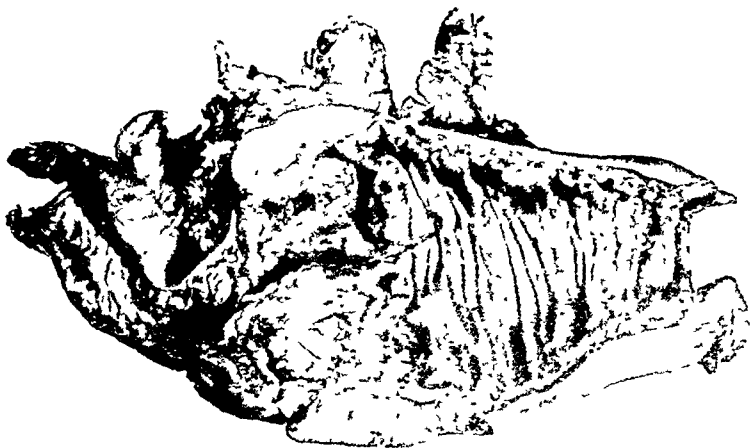


FIG 2

DISCUSSION

The chief points of interest in this case lie in the fact that the pain was epigastric, and to the left of the midline with radiation to the back, suggesting a pancreatitis, and in the fact that there was no distention of the abdomen or disturbance of bowel function, such as one would expect in partial intestinal obstruction.

The diagnosis of chronic, recurrent pancreatitis is not often made preoperatively and is usually reached only after exclusion of all other possibilities. In the absence of pancreatic stones, it is based upon a history of attacks of severe left upper quadrant pain, radiating to the back, with elevation of the serum amylase or of the blood sugar. It is interesting to note that partial intermittent intestinal obstruction can simulate chronic, recurrent pancreatitis.

FINAL DIAGNOSIS

Lymphosarcoma of small intestine with partial intermittent intestinal obstruction.

EDITORIAL

HOW MUCH DOES THE AVERAGE PATIENT UNDERSTAND OF WHAT THE PHYSICIAN TRIES TO TELL HIM?

A physician was often taken to task by his office nurse because, as she pointed out, in telling patients what was the matter with them and what they should do about it he so commonly used either medical terms or long words which they did not understand or had never even heard of. The nurse said that often, patients, after an interview with the doctor, would come to her to ask what he had been trying to say, and often when she asked them what they had understood of his instructions she found that they had gotten an idea just the reverse of what he had intended to give.

During his medical lifetime the writer has sat in at many a consultation during which he has been distressed to see that the patient was not getting much out of what the eminent specialist was saying. The reason was that the physician not only used the sort of speech which he might have used at a meeting of a medical society, but he used medical abbreviations such as B.M., E.C.G., B.M.R., K.U.B., N.P.N., or D. and C., which only a physician, and perhaps only a physician working in a particular hospital, could interpret. Worse yet, he used wrongly some of his technical words such as "pathology." The dictionary says that this means "the branch of medicine which treats of the essential nature of disease," but those of us who prefer long words to short ones have of late taken it to mean disease or a lesion. All in all, it is no wonder that the patient failed to grasp much of what was said!

It is unfortunate that today so many physicians admire the more obscure forms of technical speech, and even some editors are inclined to reject a paper if it is written in what they consider too informal and simple and Anglo-Saxon a vernacular. Young writers, perhaps hoping to impress their readers, will substitute emesis for vomiting, micturition for urination, temperature or hyperthermia for fever, or mental alienation for insanity. An amusing paraphrase for a black eye was—"a contusion of the periorbital integument, subcutaneous hemorrhage, ecchymosis of the conjunctiva and the periorbital cuticular tissues, discoloration, tumefaction and abrasion of the supramalar epidermis!"

Great lovers of long-winded obscure speech are some psychiatrists, who cultivate an almost unintelligible jargon, made up of newly coined words or old words used with new meanings. This penchant for an obscure mode of writing and talking is unfortunate because it would seem that if ever a physician needed to speak simply and plainly and with crystal clearness, it would

be when talking to those who are mentally confused. One wonders how a man who trains himself to speak in such a way that he cannot be understood by his fellow physicians can ever hope to talk clearly enough so that he can help a patient. As Wendell Muncie, the eminent psychiatrist, wrote of a recent book on psychoanalysis, "I [found it] a very severe experience in understanding!" Here, for instance, is a sentence picked at random from a book written by a nationally prominent authority.

"It is a methodological error to attempt to interpret psychologically an organic symptom which is the end-result of an intermediary chain of organic processes, instead of trying to understand those vegetative nervous influences in their relation to psychologic factors which introduce a chain of organic events resulting in an organic disturbance."

In this case one can get, after several readings, some idea of what the author was trying to say because he stuck to known words and used them in the usual ways; the real difficulty comes when a psychiatrist uses so many obscure or recently coined words that even a dictionary does not help.

All physicians who are interested in having their patients understand what they are trying to say should read an article on "The Patient's Language" written by Frederick C. Redlich and published in the *Yale Journal of Biology and Medicine* (vol. 17, 1945). Dr. Redlich asked twenty-five patients with neuropsychiatric disorders to define sixty common medical terms, such as are used at the bedside every day. None of these patients had more than a high school education, but their intelligence quotient averaged fairly high, or about 110. None of them, of course, understood medical abbreviations, such as gc. for gonorrhea or ca. for cancer. None knew what is meant by metastasis. Ninety-two per cent did not know what is meant by lues; 87 per cent could not define psychogenic, and a high percentage had no understanding of the words: lesion, prognosis, deterioration, pathology, physiotherapy and psychotherapy. Seventy-one per cent guessed wrongly at the meaning of "functional," the word that we physicians now love so much. Ninety per cent were confused as to psychopathic, and a high percentage had no knowledge of what is meant by neurologist, psychologist, psycho-analysis, nervous disease, neurosis, moron or organic. In many cases, because of this lack of knowledge, the patients were found to have been much handicapped in their efforts to get help from what was said to them by doctors and nurses.

As all wise physicians know, most persons are outraged when told that they are *nervous* because they do not understand what is implied by that. They think the word means silly, flighty, jumpy and hysterical with a large element of malingering and enjoyment of illness thrown in, and so they flare up in resentment. They say, "You mean, there is *nothing* the matter with

me?" Naturally, unless the physician can get his ideas over better than this he will never be much of a success in the treatment of functional disorders and anxiety neuroses.

Probably one of the best and most useful courses that could be given to medical students would be one in which they would be taken into the outpatient department and there taught to make themselves intelligible to immigrants who know only a few hundred words of English. Eventually, after learning what these few words are, the young physician might be able to talk to people of ordinary intelligence and schooling in such simple speech that he could usually be understood. Success along these lines would go far to improve the relations between the medical profession and the public.

Incidentally, the physician who writes for his fellows and wants his papers to be widely read will do well to use, whenever possible, short English words, rather than long ones of Greek or Latin origin. As many a physician has remarked, "When I come in tired at night after what I hope is my last call, I know I should do some reading, but my brain is so tired that it is hard for me to read a paper that is full of long technical words. At such a time it is so much easier to read something that is written simply with short, well-known words."

Those who are interested in improving their style should pick up Fowler's delightful little book, "Modern English Usage" and turn to the article, "Love of the long word." As Fowler there said, "Good English does consist in the main of short words." He quoted two stately paragraphs from Milton and Tennyson to show that out of fifty-six consecutive words fifty-two were of one syllable. The King James Bible and the Prayer Book, with all their majesty and beauty, were written with short words.

It is good to know the long words; there is a place for them, but the wise speaker and writer will never drag one in when a simpler and shorter one will serve his purpose, that is, if he wishes to be widely read and easily understood so that the message he has will travel far and have an influence on medical thought. If he writes, oblivious to his audience, or if he is reluctant to give away his knowledge, that is another matter.

A German professor was once asked why his massive book was written so vilely and unintelligibly with such long words and such long involved sentences that a page had to be read several times before any sense could be gotten out of it. He answered that he had slaved and starved for years to get the knowledge that went into that book, and he did not intend to give it freely away; anyone who wanted it would have to slave and sweat for it too!

Fortunately we physicians in America haven't much of that spirit, but we have too much of the idea that our speech should be technical and formal

and not easily understood by the uninitiated. As already intimated, this is bad, partly because it makes for hard reading by ourselves and largely because it trains us to speak so badly that we make a mess of things when we try to explain an illness to a patient. A man who habitually talks to his fellows in an involved medical slang cannot in a moment change, to talk in simple biblical English to a laborer with the gripes in his belly, a bit of wind, and a touch of the piles.

W. C. A.

COMMENT

IS ETHYLENE DISULPHONATE USEFUL IN THE TREATMENT OF ALLERGY

Of late there has been considerable talk about the value of ethylene disulphonate or Allergosil in the treatment of allergy. Several physicians have reported excellent results in more than 85 per cent of the cases. In an article in the July, 1946, number of "Minnesota Medicine," J. S. Blumenthal of the University of Minnesota, discussed this subject and pointed out that in November, 1942, the Council on Pharmacy and Chemistry of the American Medical Association was very critical about this drug. The cost was \$13.50 for one dose of 2 cc. They noted that Fisk, Small and Foord were unable to see that ethylene disulphonate had any effect in preventing allergic shock in animals.

Recently, ethylene disulphonate has been used in the allergy clinic of the University of Minnesota. The standard dose was 2 cc. Because it was stated that the solution is highly unstable and rapidly oxidizable in the presence of air, oil and other chemicals, the contents of the ampule were rapidly drawn up and injected. The drug was used in twelve cases of asthma and six of allergic rhinitis. Three injections were given at intervals of one week; and no results were seen that would warrant continuation of the treatment.

According to the report of the Council on Pharmacy and Chemistry of the American Medical Association (published August 31, 1946) the solution of ethylene disulphonate put out by the Spicer-Gerhart Company is essentially distilled water. This of course explains why some investigators have been unable to see that the drug had any effect. It does not explain so well the enthusiastic reports of some writers.

A race is now on to produce anti-allergic or antihistaminic drugs, and physicians will have to be slow in accepting everything they read about them. A drug may, for a few seconds or minutes, have an antihistaminic effect on a segment of bowel studied in the laboratory, but this need not mean that for hours or days it will ward off mucous colics, hay fever, asthma or eczema.

W. C. A.

ULCERATIVE ESOPHAGITIS DUE APPARENTLY TO A VIRUS

If only because of the possibility that a virus infection may be responsible for some cases of regional enteritis and chronic ulcerative colitis, it is worth noting and remembering that Pearce and Dagradi some time ago reported the finding of four cases of acute ulceration of the esophagus with intranuclear

inclusion bodies such as are seen in lesions due definitely to infection with a virus.

It may be significant that in two of these cases the patients died of ulcerative colitis. In the third case the cause of death was abdominal abscess formation following diverticulitis, and in the other there was a suppurative peritonitis following acute cholecystitis and an operation.

Against the idea that the virus that was associated with the esophagitis produced the ulcerative colitis was the fact that in these cases no viral bodies could be found in the colonic ulcers. Nevertheless, it would seem well during the next few years that pathologists remember these two cases of Pearce and Dagradi, and always during necropsies of patients who have died from regional enteritis and ulcerative colitis search other parts of the digestive tract for little ulcers with inclusion bodies in the floors.

W. C. A.

REFERENCES

1. PEARCE, JOHN, AND DAGRADI, ANGELO: Acute ulceration of the esophagus with associated intranuclear inclusion bodies. *Arch. Path.*, 35: 889-897 (June) 1943.

BOOK REVIEWS

NUTRITION AND DIET THERAPY. Ninth Edition. *By Fairfax T. Proudfit and Corinne Hogden Robinson.* The Macmillan Company, New York. 1946. pp. 782. Price \$3.75.

Any book that gets into the ninth edition must be good. Most of the chapters are on the dietary treatment of the several-diseases. At the end there is a large chapter on recipes.

EARLY AMBULATION AND RELATED PROCEDURES IN SURGICAL MANAGEMENT. *By Daniel J. Leithauser, M. D.* Charles C. Thomas, Publisher. Springfield, Illinois. 232 pp. Price \$4.50.

Especially in these days when hospital beds are so hard to get, this book should be of interest to every surgeon. The surgeon tends to be a very conservative person if only because he has the feeling if anything should go wrong with the patient on whom he has operated, he is likely to get severely blamed if he should have deviated in any way from recognized surgical practice. Often if one argues with him about certain practices, he will admit that they are not logical and that he cannot give a good reason for them, but they are customary and therefore he follows them.

Dr. Leithauser notes that when he first tried to publish on this subject and report his good results, no journal of surgery was willing to take his paper. Eventually, it was published in the Archives of Surgery. He began these investigations in January, 1938. However, others fifty years ago, had suggested early ambulation after surgery. Obstetricians also should know that among primitive peoples the woman who has just had a child commonly gets up the next day or the day after and does the washing.

In this book the author reports results of a series of some 2,047 cases in which there were 1,840 abdominal operations.

To show what is done, in 300 cases of so-called chronic appendicitis the patients left the hospital on the average in 2.2 days. In 795 cases of acute appendicitis they left on the average in 2.26 days. Even in the case of herniorrhaphies, 200 patients left on the average in 5.7 days. Patients who submitted to gastroenterostomy or gastrectomy were kept in on the average of from ten to fifteen days. Doubtless some patients are more amenable to this sort of treatment than are others. For instance, the reviewer remembers one day going in to see a patient who the day before had submitted to an extensive laparotomy. The man was up shaving the patient in the next bed!

ALLERGY. New Second Edition. *By Erich Urbach, M.D., and Philip M. Gottlieb, M.D.* Grune & Stratton, New York. 1946. 968 pp. Price \$12.00.

This book represents a tremendous amount of work and investigation. For years to come it will doubtless be a quarry from which many other men will dig material. There are three chapters of great interest to gastroenterologists, one

on Ingestants (page 295) one on the Allergic Diseases of the Gastrointestinal Tract (page 665) and one on the Allergic Diseases of the Liver and Gallbladder (page 684). Among foods of animal origin the authors place eggs at the top of the list and then milk. Among the cereals they place first wheat and corn and among the vegetables they place first the legumes, and then tomato, carrot, spinach, cabbage, asparagus, rhubarb, celery, onion and garlic.

For infants Hopkins found spinach and white potato to be the commonest offenders, they being exceeded only by egg, wheat, milk and orange.

The literature on the subject is well reviewed, and there are many interesting illustrations, showing lesions due to the ingestion of foods and drugs. To show that the book is up-to-date, one need only mention that there are pages on hypersensitivity to penicillin and sulfonamides.

¹FAMILIAL NONREAGINIC FOOD-ALLERGY. By *Arthur F. Coca, M.D.* Charles C. Thomas, Springfield, Illinois. 1943. pp. 160. Price \$3.00

This is a curious book which may not be entirely convincing to a good many physicians. The author's method of diagnosing an allergic food is to place the patient on a sharply restricted trial diet for four days; then other foods are added, one after the other, and their effect in increasing the pulse rate is recorded.

On page 67 Dr. Coca admits that some of his friends have advised him not to claim quite so many diseases as being due to food allergy.

Obviously, when the physician is studying any subject like food allergy, he should first be an excellent clinician of great experience so that he can keep his feet on the ground. Recently, the reviewer saw a patient who had been treated strenuously for allergy by several allergists. Unfortunately, they did not succeed in clearing up all his lesions because they were due to scabies!

ABSTRACTS OF CURRENT LITERATURE

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Associate Editor in Charge of Abstracts
Mount Sinai Hospital, New York City

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MOUTH AND ESOPHAGUS

GRIMSON, K. S., REEVES, R. J., TRENT, J. C., AND WILSON, A. D. The treatment of patients with achalasia by esophago-gastrostomy. *Surgery*, 20: 94 (July) 1946.

Achalasia, or cardiospasm, has usually been treated by diet, drugs, and intraesophageal dilatation, but some cases require surgical intervention. Neither vagotomy nor sympathectomy appear to be of value. The procedure of choice is a cardioplasty based upon the principles of the Finney pyloroplasty. It is essential that in making the anastomosis the incision be extended up through the normal sized esophagus well into the dilated portion. With satisfactory relief of the condition the dilated portion will show a marked or complete decrease to normal size. Nine cases operated upon without mortality are described.

J. DUFFY HANCOCK.

BELL, H. G. The treatment of cardiospasm by esophagogastrostomy. *Surgery*, 20: 104 (July) 1946.

Cardiospasm evidences itself by dysphagia, regurgitation, and epigastric pain of long duration. The etiology is in dispute. Comparatively few cases have been operated upon. Surgical treatment may be directed at the dilated esophagus, the cardia, the diaphragm, or the nerve supply. Dilatation is the simplest procedure and should always be tried first. Esophago-gastrostomy seems to be the most logical treatment. The approach is usually trans-abdominal but the transpleural route may be used. Reports are given of 10 cases operated upon successfully without mortality. The clinical results are most satisfactory. The technique employed resembles that of a Finney gastroduodenostomy and is well shown by suitable illustrations.

J. DUFFY HANCOCK.

ADAMS, H. D. The surgical aspects of obstructing lesions of the esophagus. *Surg. Clinics N. Am.*, 733 (June) 1946.

For chronic esophagitis with stenosis, true stenosis with stricture, and stricture due to ingestion of caustics, trauma or cardiospasm,

graduated dilatations must be done. There is serious danger of mediastinitis resulting in 100% mortality unless large doses of penicillin and mediastinal drainage are instituted. A posterior mediastinotomy should be performed as soon as possible after rupture of the esophagus.

Pulsion diverticula in the upper esophagus are best operated on by a 2-stage procedure. The first stage includes freeing and elevating the sac, allowing free drainage, relief of obstruction, and sealing of the fascial planes to the mediastinum. The second stage is the actual resection of the sac. Traction diverticula occurring in the mid-thoracic esophagus can be resected by an extra-pleural posterior mediastinotomy or even by a transpleural approach, with heavy adjuvant penicillin therapy.

Carcinoma of the esophagus necessitates subdivision according to its occurrence in the upper or the lower half of this structure. In the lower half, a left transpleural exposure is used, bringing the stomach up through the diaphragm for anastomosis, and a simple catheter gastrostomy is done with examination of nodes. In the upper half, a 2-stage procedure is used, consisting of transthoracic resection. Several months later the gastrostomy is closed and the stump of the esophagus is mobilized and utilized by use of an artificial tube connection to the upper stump or later to an antethoracic plastic skin tube.

FRANK G. VAL DEZ.

STOMACH

GILES, R. G. Roentgenological consideration of gastro-intestinal disturbances with special reference to the stomach and duodenum. *Southern Med. J.*, 39: 570 (July) 1946.

The importance of a complete investigation of every patient with indigestion or dyspepsia is stressed. In addition to a careful history such an investigation should employ a thorough physical examination, a careful X-ray study, and all the available diagnostic procedures. It is true that expert roentgenography is of more value in diagnosing organic disease of the stomach and duodenum than any other diagnostic method,

sign or symptom. The trained and careful searching roentgenologist can expect to demonstrate organic diseases of the stomach and duodenum in not more than 15-20% of the patients who complain of gastro-intestinal symptoms.

IRVING GRAY.

MOERSCH, H. J. The value of gastroscopy in the diagnosis of gastric disease. *Med. Clinics N. Am.*, 903 (July) 1946.

Gastroscopy is indicated in questionable carcinoma of the stomach; employed in close collaboration with the roentgenologist, a correct diagnosis may be established where use of either method alone is inconclusive. The method is of minor importance in determining operability of gastric cancer. In the differentiation between benign and malignant gastric ulceration gastroscopy is valuable not only in diagnosis but in determining response to treatment, because the roentgenographic evidences of gastric ulcer disappear more rapidly than the gastroscopic evidence. Gastroscopy is by far the most valuable method in the diagnosis of gastritis. Erosive gastritis is manifested by multiple small superficial erosions. It is regarded by some as a fore-runner of gastric ulcer and is frequently associated with gastric bleeding. Gastroscopy may offer the explanation for symptoms persisting after gastric operation. One can usually obtain a satisfactory view of the new stoma and adjacent jejunum. In unexplained gastric bleeding one may detect a previously unidentified small gastric ulcer or carcinoma, erosive gastritis, gastric varices, benign tumor or foreign body.

S. G. MEYERS.

BOWEL

NORRIS, J. C. Aberrant pancreas in the duodenum. *Southern Med. J.*, 39: 549 (July) 1946.

The author reports the finding of a tumor in the wall of the duodenum, which on histological examination was found to be pancreatic tissue. The size of this tumor was 2 by 1.5 cm. in diameter. This well-nourished male, 27 years of age, died of gun-shot wounds with severe injuries in various parts of his body; nothing is known of the patient's related clinical complaints prior to death.

Blood chlorides and total proteins were normal and there was no dextrose present in the urine. Because of the rarity of the growth, the author reports this case.

IRVING GRAY.

CROMAR, C. D. L. Benign ulcer of the caecum. *Am. J. Dig. Dis.*, 13: 230 (July) 1946.

This clinician reported a case of benign ulcer of the caecum, operated upon in the belief that the patient was suffering from appendicitis. A hemicolectomy was performed because the lesion was thought to be malignant. The literature was reviewed which included the etiology, choice of operative procedure, and the mortality rate.

H. J. SIMS.

CATTELL, R. B. AND COLCOCK, B. P. Congenital megacolon. *Surg. Clinics N. Am.*, 644 (June) 1946.

The symptoms begin shortly after birth, but by the time treatment is undertaken, hypertrophy of the bowel wall occurs with fibrosis of all its coats, particularly the muscularis. Lumbar sympathectomy alone offers little chance of permanent relief, but if employed it should be reserved for the milder cases with diffuse dilatation.

Six patients, operated upon at the Lahey Clinic from 1940 to 1945, are here reported. Ages ranged from 8 to 17 years. Bilateral lumbar sympathectomy was performed exclusively in 2 patients with good immediate results, but they had recurrence of their symptoms within a year. Subtotal colectomy is the treatment of choice for advanced cases of congenital megacolon, and was done in 2 other cases. Bilateral lumbar sympathectomy with segmental resection of a localized megacolon was performed in the remaining 2 cases. Lumbar sympathectomy should not accompany subtotal colectomy.

FRANK G. VALDEZ.

GAUSS, H. Present trends in mucous colitis. *Am. J. Dig. Dis.*, 13: 213 (July) 1946.

The author contends that mucous colitis is definitely associated with psychoneurotic states which manifest high tension, anxiety, submerged fear complexes, etc. The causes

are manifold and complications are prolonged. The common symptoms are mucus in the stools, localized or diffuse abdominal pain, constipation, flatulence; also numerous other local and constitutional symptoms. The principal X-ray sign is the string sign, which usually occurs in a descending colon of rope-like characteristics. It must be borne in mind that there is a cycle in which psychic states give rise to somatic symptoms, and these in turn to other psychic states, producing an endless procession of reciprocal factors. The prognosis is always guarded. The disease is never fatal; cures are sometimes obtained but recurrences are frequent; however, it is apt to be chronic and persist for years at a time.

II. J. SIMS.

KAY, J. H. AND LOCKWOOD, J. S. Experimental appendical peritonitis. I. The prognostic significance of certain hematologic factors, especially the prothrombin time. *Surgery*, 20: 56 (July) 1946.

Recent definite reduction in mortality can not be attributed entirely to the sulfonamides and penicillin, as the bacteria most commonly found are not especially susceptible to the bactericidal or bacteriostatic action of these agents. Intestinal decompression and the maintenance of fluid, electrolyte, and blood are of great importance, and mechanisms other than bacteriostatic effects may be involved in the protective action of penicillin. In order to study particularly the disturbances in hemodynamic equilibrium, experimental appendical peritonitis was induced in dogs and studies were made of nonprotein nitrogen, protein concentration, chloride, sodium and potassium, calcium, oxyhemoglobin, blood and plasma specific gravity, sedimentation, hematocrit, prothrombin time, fragility of red blood cells, and the identification of bacterial organisms.

The most significant finding was the importance of prolonged prothrombin time. This was associated with both respiratory distress and usually a fatal outcome. This disturbed clotting mechanism is related to the hemorrhagic changes in the peritoneum, liver, and lungs and may be due to the injury of the liver parenchyma by anoxia or bacterial toxemia. Before accepting this ex-

planation as entirely satisfactory the authors contemplate further investigation of the circulating proteolytic and antiproteolytic factors.

J. DUFFY HANCOCK.

CATTELL, R. B. AND BOEHME, E. J.
Chronic ulcerative colitis complicated by carcinoma of the colon and rectum. Surg. Clinics N. Am., 641 (June) 1946.

Nine cases of malignancy in the colon and rectum associated with chronic ulcerative colitis were noted in the past 7 years. In the majority of these the ulcerative colitis had been present for many years before its recognition.

Two cases are presented in detail. The first is that of a 27 year-old man with ulcerative colitis of 13 years duration. A complete colectomy was performed in 3 divided operations, and an unsuspected adenocarcinoma with foci of carcinoma simplex was found. The second case was a 53 year-old male with a history of ulcerative colitis dating back 18 years. On operation for an ileostomy, a fixed mass was found at the hepatic flexure which revealed a mucinous carcinoma. Roentgenologic study had not revealed the lesion. Paramount symptoms were weight loss and increase in bloody stools.

Follow-up study of all ulcerative colitis patients is necessary, and earlier surgical intervention than they now receive, once warning symptoms appear. Broadening of the indications for colectomy is urged.

FRANK G. VAL DEZ.

KIEFER, E. D. Chronic ulcerative colitis: Diagnosis and medical treatment. Surg. Clinics N. Am., 631 (June) 1946.

The outstanding symptom is frequently a rectal discharge of bloody mucus. Commonly, there are 2 types of bowel movements: (1) diarrheal stools consisting of liquid feces with more or less blood, and (2) rectal discharges which consist of mucus, blood, and pus. Systemic symptoms are variable. Ulcerative colitis is mainly a disease of young adults. Its diagnosis depends on the correlation of proctosigmoidoscopic findings and roentgenography of the lower bowel. Differential diagnosis involves consideration of cancer of the rectum and colon,

bacillary and amebic dysentery, tuberculous enterocolitis, lymphopathia venereum, and regional ileitis.

In treatment, control of diarrhea may be difficult if not practically impossible at times. Use of 1 to 1.5 grains of papaverine every 4 hours may be effective in relieving abdominal cramps. Sedatives may aid in the reduction of bowel movements. Treatment of malnutrition involves the use of a high protein diet, vitamin supplements and blood transfusions in the case of anemia and hypoproteinemia. Treatment of sepsis centers about the use of the soluble and poorly soluble sulfonamides. Non-specific fever therapy may be of some benefit. The place of psychotherapy in management is emphasized.

FRANK G. VAL DEZ.

ADAMS, R. AND MILLER, W. H. Surgical treatment of intestinal tuberculosis. Surg. Clinics N. Am., 656 (June) 1946.

Out of 100 cases of intestinal tuberculosis seen at the Lahey Clinic, 19 patients received surgical treatment. Ages varied from 16 to 66 years. Abdominal fistulas were closed in 4 instances, with recurrence in 3. Resection of the right colon, with the formation of a Mikulicz ileo-transverse colostomy and secondary closure, was done in 7 cases. Four patients were well after 9 months to 3.5 years. Resection of the right colon with primary ileocolic anastomosis was done in 3 cases with a satisfactory result in 2 of them (3 months and 8 months duration). There were 2 resections of segments of small bowel with primary anastomosis, resulting in a recession of symptoms for one year. Two side-tracking ileo-transverse colostomies were done with poor results. There was one resection of the sigmoid and an associated painful abscess, with the formation of a permanent colostomy.

In the presence of active intestinal tuberculosis a diversionary colostomy should be done, and sanatorium care instituted until the tuberculous process has been quiescent for at least 1 year. Patients with active pulmonary lesions should first have arrest of this condition before the intestinal lesions are attacked.

FRANK G. VAL DEZ.

WILLIAMS, A. G. AND FODDEN, J. H. Sac-
cular diverticulosis of the jejunum due to
reticulum-cell sarcoma. *Brit. J. Surg.*,
34: 57 (July) 1946.

Reticulum-cell sarcoma of the duodenum
and jejunum is quite rare. It arises within
the lymph follicles of the submucosa. These
globular tumor masses destroy the adjacent
stroma and push into the lumen of the bowel
causing either dilatation or constriction. A
central necrosis of the mass with sloughing
of the overlying mucosa results in the for-
mation of secondary or tumor pouches (di-
verticula).

The case presented was subjected to re-
section, but within a few months vertebral
column metastasis appeared and death oc-
curred. The article is illustrated with an
X-ray photograph and several photomicro-
graphs.

J. DUFFY HANCOCK.

MARKBY, C. E. P. Derangement of midgut
rotation producing volvulus. A report of
two cases. *Brit. J. Surg.*, 34: 80 (July)
1946.

Derangement of midgut rotation in the fetus
may occur in the first, second, or third stage.
Those in the first are extremely rare and are
evidenced by extroversion of the cloaca.
Those of the third stage are the most com-
mon and present non-descent or abnormally
high fixation of the cecum. Derangement
of the second state, where there should be a
180 degree counter clockwise rotation, may
be due to nonrotation, inverse rotation, or
malrotation. When such occurs, volvulus
may result and usually evidences itself in the
first few days of life.

Two cases are reported, one due to non-
rotation and one to inverse rotation. In
the former a side-to-side duodenojejunos-
tomy was performed successfully. In the
latter the volvulus was unwound and a ceco-
stomy done, but a fatal pulmonary embolus
occurred.

J. DUFFY HANCOCK.

LIVER AND GALLBLADDER

COPLEMEN, B. Emptying of the normal
gallbladder with Priodax. *Radiol.*, 47:
30 (July) 1946.

When the gallbladder is visualized with

tetraiodophthalein, a fat meal usually pro-
duces prompt and vigorous emptying in the
normal individual. In more than half of
the cases without stones, the cystic and
common ducts may be visualized. In a
small number of cases, demonstration of the
hepatic duct or even its radicles may aid the
diagnosis of biliary dyskinesia. The de-
crease in size of the gallbladder also helps
in the differential diagnosis between gas
shadows and small non-opaque stones.

Priodax, while producing a dense gall-
bladder shadow, appears to interfere with
gallbladder emptying and the visualization
of the bile ducts. In comparison with tetra-
iodophthalein, priodax acts like a sympathi-
comimetic drug.

FRANZ J. LUST.

JUNET, R. AND ALPHONSE, P. L'hépatite
épidémique et ses séquelles (Epidemic
hepatitis and sequelae). *Gastroentero-
logia*, 71: 4 (1946).

Epidemic hepatitis, a disease which was very
common from 1939 to 1946, usually runs a
benign course. Fatal termination is rare
and usually is due to atrophy of the liver.
The disease at times runs a prolonged or
remittent course, and disorders which are not
primarily associated with liver disease may
occur as sequelae. These latter are com-
paratively rare.

The commonest sequelae of infectious
hepatitis are manifestations of liver dys-
function, gall bladder or gastroduodenal
disorders. Non-specific gastrointestinal
symptoms without objective findings are fre-
quently present and are seen in individuals
with neurovegetative dystonia. Various
disturbances of the nervous system, pan-
creas, respiratory system, circulation, spleen,
and even kidneys, may also follow acute
hepatitis. Disturbances in the metabolism
of proteins, sugars, fats, iron, and vitamins
may also be found by laboratory study.
The general well-being of the individual is
affected and there is frequently fatigue and
inability to work. Attempts to demonstrate
a cortico-adrenal insufficiency have not been
successful.

CHARLES FLOOD.

CRILE, G., JR. AND BROWN, A. Pain and
fever arising from the common bile duct

and not associated with jaundice. Report of two cases of choledocholithiasis treated by choledochostomy and one of post-cholecystectomy biliary dyskinesia relieved by vagotomy. *Cleveland Clinic Quart.*, 13: 147 (July) 1946.

Two cases are reported of stones in the common duct in the absence of stones in the gall bladder. Chills and fever were produced for a year and a half in one, and only severe intermittent biliary colic without jaundice in the other. They were both relieved by choledochotomy and removal of the stones. In the majority of cases in which there are common duct stones without jaundice, it is probable that the pain is caused by stones in the gall bladder rather than in the common duct.

A third case of post-cholecystectomy biliary dyskinesia, relieved by sub-diaphragmatic vagotomy, is reported. The bile duct was grossly normal in this case. It is suggested that this procedure may prove more useful than denervation of the common duct and section of the splanchnic nerves, but no conclusions are warranted until further evidence is accumulated.

FRANK G. VAL DEZ.

WADE, L. J. Liver function tests. *Am. J. Clin. Path.*, 16: 426 (July) 1946.

Liver function tests are classified according to particular functions of that organ, because none of them give all-inclusive information regarding disturbance of liver function, or pathological changes taking place in the organ.

(1) Of the tests based upon secretory and excretory functions of the liver, the van den Bergh quantitative determination of urobilin or urobilinogen in urine and stools often gives valuable diagnostic information. It is based upon the transformation of hemoglobin into sodium bilirubinate, which is secreted into the intestinal tract from the liver. On its reabsorption into the circulation it is excreted by the kidney. The excretion of bromsulfalein apparently depends upon the same mechanism as that of bilirubin. The serum alkaline phosphatase is also used, and is elevated in obstructive jaundice since bile contains alkaline phosphatase.

(2) Of the tests based upon the de-

toxifying function of the liver, the hippuric acid synthesis is most widely used. With it is used simultaneously the PSP test for renal function.

(3) Of the tests based upon the role of the liver in carbohydrate metabolism, the galactose tolerance test is probably the best, although other reducing substances may interfere.

(4) The role of the liver in protein metabolism is important, and changes in the quality and quantity of the plasma proteins are commonly associated with liver dysfunction. Determination of the albumin-globulin ratio is of value, as is also the cephalin-cholesterol flocculation test.

(5) Of the tests based upon the role of the liver in lipid metabolism, the plasma cholesterol is usually increased in the presence of common duct obstruction. In early stages it usually parallels the degree of hyperbilirubinemia.

A plea is made for a proper selection of tests, designed to answer particular questions, rather than a haphazard use of any or all tests. In suitable cases the needle biopsy method is of value. However, often the severity and the extent of the liver damage cannot be measured adequately by the techniques available.

N. W. JONES.

LONCHARICH, J. A., TANTURI, C. A. AND BANFI, R. F. The protective action of sulfanilamide in chloroform hepatitis. *La Prensa Medica Argentina*, 33: 1425 (July) 1946.

The authors studied the protective action of sulfanilamide in chloroform hepatitis. They measured the hepatic insufficiency by the prothrombin activity of the blood, using the method of Tanturi and Banfi. The amount of sulfanilamide in the blood was determined by Banfi and Loncharich's method. Chloroform was given during 1 hour to 16 dogs receiving no food for 3 days. Eight of them received 150 mg. of sulfanilamide per kg. during 4 to 5 days before the anesthesia, and the other 8 animals served as controls. Five of the 8 control animals died within 48 hours, but all the animals that received sulfanilamide survived. Hypoprothrombinemia due to the chloroform

nitoxication was much less intense in the treated animals. One dog that received sulfanilamide 1 hour before the anesthesia did not get any protection.

ALOYSIO FARJA.

JOHNSTONE, G. A. AND OSTENDORPH, J. E.
Cholecystitis with perforation. *Arch. Surg.*, 53: 1 (July) 1946.

Thirty-two instances of perforation of the gall-bladder were found in a review of 12,000 consecutive, routine necropsies. This corresponds to an incidence of 0.26%, or approximately one out of every 375 cases of death from a perforated gall-bladder coming to necropsy. Stones were present in 84% of these cases. Among this group of patients 14 had free perforations with acute generalized peritonitis, and 19 had localized perforation. In 49% perforation occurred but was unrecognized and not diagnosed until necropsy. In an additional 105 patients operated upon for acute cholecystitis the mortality was shown to increase in proportion to the time of operative delay. This was 2.9% for patients operated upon within 48 hours, and it rose to 11.4% when this interval mounted to 7 days or more.

The authors conclude that peritonitis following perforation is an inherent danger of acute cholecystitis, and therefore so-called medical or conservative treatment is not without hazard. Once the diagnosis of acute cholecystitis is made, particularly in the elderly patient, surgical intervention should take place as early as is consistent with adequate preparation of the patient and operating facilities. Also, interval cholecystectomy should be done in cases of recurrent chronic cholecystitis, thereby removing the possibility and dangers of progressive disease.

C. WILMER WIRTS, JR.

SYMMERS, D. AND SPAIN, D. M. Hepar lobatum. Clinical significance of the anatomic changes. *Arch. Path.*, 42: 64 (July) 1946.

A statistical study of 102 cases of this form of syphilitic cirrhosis, found in 23,792 necropsies at Bellevue Hospital over a period of 30 years, is given. In 314 cases of late acquired syphilis coming to autopsy, hepar

lobatum was noted in 50 cases (16%). It occurred more frequently in men than in women, more frequently in the white race than in negroes. The average age was 38.5 years, but varied from 19 to 80 years. The diagnosis of syphilitic cirrhosis of the liver was made during life in but 3 cases. The organ was palpable below the costal arch in 18 cases. The spleen was palpable in 13 cases. Jaundice was present in 35 cases, ascites in 32, and esophageal varices in 15. An irregular fever, varying from 100 to 106° F, was present in 12 cases. The weight of the liver varied greatly, from 608 to 3,450 g. Its average weight was 1556 g., i.e. quite normal. In 55 cases the spleen averaged 538 g. in weight, but again the weight varied markedly—from 60 to 1980 g. Two additional cases of the rare form of splenomegaly occurring in late acquired syphilis were found, which makes 11 cases thus far reported in the literature.

The clinical diagnosis of hepar lobatum depends upon the history of syphilis, the positive Wassermann reaction, associated syphilitic lesions, jaundice, ascites, enlarged spleen, and the response to appropriate treatment. Liver biopsy may be made when this organ extends below the costal arch.

N. W. JONES.

PANCREAS

PRESENT, A. J. Aberrant pancreas. *Am. J. Roent. Rad. Therapy*, 56: 55 (July) 1946.

Aberrant pancreatic tissue is observed in various parts of the abdomen. It is not infrequently found in the gastrointestinal organs. It most frequently occurs near the pancreas and is more commonly seen in the stomach, duodenum, jejunum, ileum, and in Meckel's diverticulum. Two cases of aberrant pancreas occurring in the antrum of the stomach are reported by Present. Both occurred in males aged 33. In both cases there was vomiting and in one hematemesis. In one case the condition produced a large filling defect in the prepyloric region, causing delayed emptying of the stomach. In the other, a polypoid defect was seen in the antrum of the stomach.

MAURICE FELDMAN.

ULCER

LYONS, S. C. AND SINCLAIR, L. G. Perforated peptic ulcers in naval personnel.

Southern Med. J., 39: 575 (July) 1946.

The diagnosis of ruptured peptic ulcer is usually not difficult and can be made clinically in most cases. Prompt operation is the keynote of success. The procedure should include only simple closure of the ulcer; additional surgery, if indicated, should be performed at a later elective date. Postoperative therapy is based chiefly on constant in testinal decompression, chemotherapy, and the judicious use of parenteral fluids, including plasma and whole blood. After recovery from the operation, patients whose symptoms persist, and in whom roentgenologic study shows persistence of ulceration, should be promptly discharged. Patients who present only minor symptoms can be tentatively returned to limited duty. Patients who are free from symptoms can be returned to full duty, with the reasonable expectation that they will remain well and will prove useful members of the service.

These conclusions are based on a survey of the recent British, Canadian and American literature and upon an analysis of 22 personally observed cases of ruptured peptic ulcer in a naval training camp. Of 20 men observed sufficiently long to permit conclusions, 12 were returned to full and 3 to limited duty, and all have been serving without subsequent disability for periods ranging from 7 to 30 months. A unique feature of the series is that all ruptures occurred shortly after the men were inducted into service, in 14 instances between 7 days and 2 months after induction.

IRVING GRAY.

MARSHALL, S. F. The problem of gastrojejunal ulcer with illustrative case reports.

Surg. Clinics N. Am., 751 (June) 1946.

Three types of gastric surgery contribute to the production of gastrojejunal ulcer: (1) gastroenterostomy, (2) the Finsterer operation which allows the ulcer to remain in situ, and (3) an inadequate partial resection of the stomach.

Gastroenterostomy should be restricted to those cases in which there is marked scar

tissue obstruction of the pylorus with accompanying low acid values, or in those cases with high risk of a more radical procedure. Failure to remove a major portion of the stomach in doing a partial gastrectomy fails to reduce the gastric acidity materially and leads to a high percent of recurrent ulcers. Two-thirds to three-fourths of the stomach should be resected, in an effort to obtain a relative anacidity. The Finsterer operation, which allows that portion of the pyloric end of the stomach containing an ulcer to remain in situ after transection of the stomach above the ulcer, is rarely employed. It should be used only in the case of ulcers very low in the duodenum, and provided the line of transection above the ulcer is through the duodenum and well beyond the pylorus. There has been a high incidence of gastrojejunal ulcers occurring in this type of resection, where a portion of the pyloric area has been allowed to remain.

Illustrative cases of recurrent ulcers following the above inadequate procedures are included.

FRANK G. VAL DEZ.

PROCTOLOGY

COLCOCK, B. P. Injuries of the colon and rectum. *Surg. Clinics N. Am.*, 665 (June) 1946.

If the peritoneal cavity has been entered by a lacerating or perforating wound of the abdominal wall, laparotomy and thorough examination of the abdominal viscera are imperative. The diagnosis of intra-abdominal injury without external wounds may be difficult. Any wound of the colon must be handled in such a way as to prevent further leakage of intestinal content into the peritoneal cavity. There must be no marked impairment of the bowel lumen following treatment, and there should be as little shock induced as possible. In the treatment of injuries of the rectum, a proximal colostomy should be performed, with adequate drainage of the contaminated perirectal tissues.

FRANK G. VAL DEZ.

SURGERY

DENNIS, C. AND VARCO, R. L. Neoplastic biliary obstruction. An improved type

of radical pancreaticoduodenectomy for ampullary and pancreatic cancers. *Surgery*, 20: 72 (July) 1946.

The history of the development of radical pancreaticoduodenectomy for ampullary and pancreatic cancers is discussed and illustrated. It is suggested that a one-stage operation is preferable, that an ascending cholangitis can be best prevented by a long jejunal loop for biliary anastomosis, thus avoiding reflux of intestinal contents, and that pancreatic secretion is of sufficient importance to be conserved. An operation of improved simplicity is described and illustrated. A long transverse incision with a vertical upward extension from the center gives satisfactory exposure. Dissection of the portal vein and superior mesenteric vein is facilitated by coagulation of the numerous fine tributaries. Vascular anomalies are fairly frequent and of extreme importance. Instead of the usual 4 or 6 suture lines only 3 are required in this University of Minnesota operation. The distal third of the stomach, all of the duodenum, the first 15 cm. of the jejunum, $\frac{3}{4}$ of the common duct, and the head, uncinat process, and neck of the pancreas are excised. The gall bladder is removed and an end-to-end anastomosis made between the jejunum and the common bile duct or common hepatic duct, after the jejunum is brought through the right side of the transverse mesocolon. As the jejunum passes the cut end of the pancreas it is anastomosed to the pancreatic duct. Forty centimeters down the jejunum a retrocolic Polya gastrojejunostomy is performed. Drains are placed adjacent to the pancreatic and biliary anastomoses.

Inoperable lesions may be treated by an end-to-end cholecystojejunostomy or choledochojejunostomy with a modified Roux Y-plasty of the intestine and a gastrojejunostomy.

J. DUFFY HANCOCK.

PANNETT, C. A. Resection of the head of the pancreas. *Brit. J. Surg.*, 34: 84 (July) 1946.

A comparatively simple type of resection of the head of the pancreas for carcinoma is presented and illustrated by two case reports. It is a one-stage procedure.

The third portion of the duodenum is exposed by dissecting off the hepatic flexure of the colon and pushing the large bowel downward after having opened the lower peritoneal sac. The pylorus is freed and cut across just proximal to the opening; the distended gall-bladder is aspirated and then closed. The duodenum is mobilized and with the head of the pancreas is lifted off the vena cava and turned to the left, exposing the common duct which is divided and lightly clamped. The neck of the pancreas is cut across and the duodenum excised just to the right of the superior mesenteric vessels. After invagination of the distal stump of the duodenum, the first portion of the jejunum is carried in front of the transverse colon to the right side of the abdomen. Into this loop of jejunum are implanted proximally the common duct, then the stump of the pancreas, and distally the end of the stomach. A drainage tube is inserted into the region of the implanted portion of pancreas

(or the invaginated portion if the pancreas is not implanted).

J. DUFFY HANCOCK.

PHYSIOLOGY: MOTILITY

GREGORY, R. A. Changes in intestinal tone and motility associated with nausea and vomiting. *J. Physiol.*, 105: 58 (July) 1946.

The general features of the behaviour of the upper parts of the alimentary tract during nausea and vomiting are well known, but the associated disturbances of tone and motility in the lower intestines have received comparatively little attention. The observations and experiments reported here show that in unanaesthetized dogs the nausea and vomiting produced by minimal doses of apomorphine are associated with a definite sequence of changes in intestinal tone and motility of antral origin. These were recorded by a balloon and water manometer method from Thiry-Vella loops of the upper jejunum in dogs. The first signs of nausea are accompanied by a rapid inhibition of intestinal tone and motility, followed by an equally rapid increase in tone, which may be maintained for several seconds before retch-

ing occurs. After this, normal tone and motility are resumed. This response was abolished by denervation of the mesenteric pedicle to the loop; this and other arguments lead to the conclusion that the response is of nervous reflex origin and probably results from the excitation of central autonomic mechanisms.

ALBERT CORNELL.

BOZLER, E. The relation of the action potentials to mechanical activity in intestinal muscle. *Am. J. Physiol.*, 146: 496 (July) 1946.

Differential potentials were recorded from the small intestine, isolated and in situ. In the rabbit and dog they show an R and T wave. Brief spikes are usually present between these two slow phases. The results agree with those obtained for ureter and stomach. Monophasic potentials were recorded directly from muscle strips. Their shape agrees well with those which are derived mathematically from differential potentials. They show a long phase of sustained negativity, like that in other visceral muscles and the heart. In small muscle strips each potential is followed by a contraction, but large variations in the mechanical response are accompanied by only slight changes in the magnitude of the monophasic potential. Adrenaline stops electrical activity only in very high concentrations. Mechanical activity may be so much reduced that it becomes invisible, but it does not disappear entirely as long as action potentials are present. In the guinea pig the potentials consist of spikes alone. Their frequency is closely related to the magnitude of the contraction.

ARTHUR E. MEYER.

PHYSIOLOGY: ABSORPTION

BIRCHALL, E. F., FENTON, P. F., AND PIERCE, H. B. Gastric emptying and intestinal absorption of dextrose solutions. *Am. J. Physiol.*, 146: 610 (July) 1946.

The amount of dextrose emptied from the stomach was greater with large volumes of dilute dextrose solutions than with small volumes of concentrated solutions, the amount of dextrose fed being constant. The

rate of absorption was somewhat greater from the more concentrated solutions of small volume. Emptying and absorption were greater from large than from small volumes of identical concentration. Emptying and absorption were greater from concentrated than from dilute solutions of identical volume.

ARTHUR E. MEYER.

METABOLISM AND NUTRITION

DUELL, H. J., JR. Studies on the comparative nutritive value of fats. IX. The digestibility of margarine fat in human subjects. *J. Nutr.*, 32: 69 (July) 1946.

Margarine fat composed of hydrogenated domestic vegetable oils was found to be digested to the extent of 97%, on the average, by normal men and women—which value is identical with that obtained in three tests on butter fat. There was no evidence of any unpleasant physiological effects when a maximum of 111 g. of margarine fat was ingested daily.

ARTHUR E. MEYER.

HATHAWAY, M. L. AND LOBB, D. E. A comparison of riboflavin synthesis and excretion in human subjects on synthetic and natural diets. *J. Nutr.*, 32: 9 (July) 1946.

Three women were kept on a synthetic diet containing 1.09 mg. riboflavin daily for 7 weeks, and after one month were placed on a natural diet containing 1.33 mg. riboflavin per day. Daily urinary riboflavin values for the three subjects averaged 165, 152, and 161 μ g. on the synthetic diet, and 174, 229, and 210 μ g. on the diet of natural foods. The 1-hour fasting urinary excretions of riboflavin varied from 3.7 to 10.9 μ g., with average values for the three subjects of 5.9, 7.1 and 7.8 μ g. Urinary riboflavin excretion showed no relation to urinary volume. Fecal riboflavin excretions on the diet of natural foods were 3.7 to 3.8 times greater than those obtained on the synthetic diet. On the diet of natural foods, total riboflavin excretions were 2.8 times greater than on the synthetic diet for all three subjects, and for two subjects it exceeded the intake.

ARTHUR E. MEYER.

HATHAWAY, M. L. AND STROM, J. E. A comparison of thiamine synthesis and excretion in human subjects on synthetic and natural diets. *J. Nutr.*, 32: 1 (July) 1946.

Three women were kept on a synthetic diet containing 1 mg. thiamine daily for 7 weeks, and after one month they were placed on a natural diet containing 0.84 mg. thiamine per day. Daily urinary thiamine values averaged 116, 113, and 147 μ g. on the synthetic diet, and 90, 91, and 112 μ g. on the natural diet. The average values for daily excretion of "free" thiamine in the feces were 17, 15, and 13 μ g. on the synthetic diet, and 25, 49, and 35 μ g. on the natural diet. "Combined" thiamine content of the feces was 2.4, 5.1, and 4.5 times higher on the natural than on the synthetic diet, suggesting that the latter was less favorable for bacterial synthesis of thiamine than the natural diet. Fecal synthesis of thiamine does not seem to be an important factor in the thiamine economy. The excretions of thiamine by these subjects, and their apparent well-being on thiamine intakes of 0.84 to 1.00 mg., justify the lowering of the recommended daily allowance for women to 1.1 or 1.2 mg. per day.

ARTHUR E. MEYER.

DAVIDSON, C. S., WILKE, H. L., AND REINER, P. J. A nutritional survey of starvation in a group of young men. *J. Lab. Clin. Med.*, 31: 721 (July) 1946.

A nutritional survey was made of 171 German prisoners who had been on a diet averaging 750 Cals. per day for 2 to 3 months. The estimated intake per day included about 40 g. of protein, 120 g. of carbohydrate, 17 g. of fat, 6,250 international units of vitamin A., 0.62 mg. of vitamin B, 0.64 mg. of vitamin B₂, 8.6 mg. of niacin, and 10 mg. of vitamin C. All of the men were wasted, the average weight being 13 kg. below U. S. standards. Seventy percent of them were more than 10 kg. below the standard. Most of the men had lethargy, a stooped posture, and weakness. Common symptoms included syncope, joint pains which were prominent in the knees but not correlated with edema, recurrent diarrhea, and generalized pigmentation.

Clinical evidence of vitamin deficiency was generally lacking. Thirty-two per cent of the men were observed to have the follicular hyperkeratosis thought to be related to vitamin A deficiency. A few instances were seen of circumcorneal injection, color change or papillary atrophy of the tongue. A condition resembling acrocyanosis was observed in the distal extremities of many men, and was associated afterward with parasthesia. Edema, probably of nutritional origin, was observed in 24%. Hypoproteinemia was common but was not correlated significantly with the edema. Only two men had a hemoglobin below 10 g. per 100 cc. of blood.

EDGAR WAYBURN.

KEELE, K. D. A study of the onset and cyclic development of the sprue syndrome. *Brit. Med. J.*, 4464: 111 (July) 1946.

This study is based upon a series of 680 British soldiers with sprue observed in India during the years 1943-45. The symptoms of onset consist of anorexia, vomiting, diarrhea, weakness, and loss of weight. After several weeks there appear glossitis, cheilosis, abdominal distension, and scaling of the skin. At this time flatulence and heartburn increase and the initial symptoms diminish or disappear. The appetite returns to normal, diarrhea declines or is followed by constipation, and the patients gain weight. In untreated cases the remission of diarrhea and return of appetite result in overeating which leads to recurrence of diarrhea. During such relapses the glossitis and distension subside but weight loss is rapid. This cycle may be continued with progressive loss of weight and the development of malnutrition.

The transition from relapse to remission may be slow, with a mixed symptomatology. During relapse, dehydration is responsible for some of the clinical features. Barium meal examination reveals gross obliteration of the intestinal mucosal pattern. Absorption of fat, carbohydrate, protein, water, and salts is markedly diminished.

During remission many of these defects remain for at least 1 or 2 months in spite of rapid gain in weight and marked clinical improvement. The macrocytic anemia is present at the onset in most cases. The

degree of anemia is not correlated with the degree of glossitis or achlorhydria. Liver therapy has less effect on the anemia than on other aspects of sprue; reticulocytosis is poor and delayed. Macrocytosis, with or without anemia, persists until weight reaches normal. Absorption of fat and sugar returns to normal only after 1 or 2 months, with or without liver therapy. Early in remission, however, improvement appears to occur in protein and water absorption, particularly with parenteral liver therapy. Signs which may be interpreted as those of a deficiency of vitamin B occur at transition from relapse or in early remission. Remission is not to be considered as synonymous with cure.

JOSEPH B. KIRSNER.

PHARMACOLOGY

✕ BARGEN, J. A. The use of the newer sulfonamides and antibiotics in intestinal diseases. *Med. Clinics N. Am.*, 919 (July) 1946.

In chronic ulcerative colitis azosulfamide (neoprontosil), sulfathiazole, sulfadiazine, sulfaguanidine, succinylsulfathiazole (sulfasuxidine) and phthalylsulfathiazole (sulfathallidine) have been found to be effective in selected cases. The drugs should be administered for two weeks, stopped for a week, and then resumed. Phthalylsulfathiazole gives rise to only an occasional toxic reaction and the therapeutic response is more sustained than with the other drugs. Successive use of several drugs may be more effective than a single drug and simultaneous use of two drugs may result in synergistic action. The author mentions a small series of cases which improved at least temporarily on carboxythiazole (sulfacrizole) where other drugs of this series had failed. Penicillin has been used with some success in the acute fulminating forms where the disease process is active, and secondary fibrosis is not marked. Streptomycin has not been given an adequate trial in chronic ulcerative colitis; in a few patients the preliminary results were not encouraging. In regional ulcerative colitis and regional enteritis succinylsulfathiazole is the drug of choice. It is used in preference to operation during the acute stage, and preliminary to

operation in advanced cases. In acute diverticulitis the use of succinylsulfathiazole or phthalylsulfathiazole has materially shortened the attack. The drug does not replace surgical treatment where indicated, but enables operation to be done more safely. These two drugs have been valuable in the routine pre-operative program for patients with intestinal fistulae and intestinal neoplasms; with other pre-operative measures a remarkable reduction in mortality has resulted.

S. G. MEYERS.

ANATOMY

FRIEDMAN, S. M. The position and mobility of the duodenum in the living subject. *Am. J. Anat.*, 79: 147 (July) 1946. The position of the duodenum was the subject of study in 454 roentgen examinations. Concerning the high point of the first part of the duodenum in the prone position, it was opposite the L-1 or L-2 in the majority (82%) of patients. After the age of 50 it tended to shift to L-2. The whole duodenum moves downward but the third part tends to lag. The duodenum tends to contract and become more concave with age.

Concerning the excursion of the duodenum with the stomach filled, shifting from prone to upright, the maximum downward excursion of the high point of the duodenum was 2 vertebra, and the mean downward shift was 0.9 vertebra. The duodeno-jejunal flexure represents the most fixed point of the duodenum. It migrated upward with the whole duodenum, from 1 to 2½ vertebra; the maximum downward movement was 1 vertebra.

MAURICE FELDMAN.

MISCELLANEOUS

FELSENFIELD, O., AND YOUNG, V. M. The correlation of intestinal protozoa and enteric microorganisms of known and doubtful pathogenicity. *Am. J. Dig. Dis.*, 13: 232 (July) 1946.

This clinician made a study of 404 patients with amebic dysentery, 39 cases of salmonellosis and bacillary dysentery, 13 of mixed infections, and 830 cases of diarrhea of unknown origin in which no microbes could be

found. Mathematical evaluation of his statistics showed that not only *Salmonella*, *Shigella*, *E. histolytica*, and *G. lamblia*, but also *D. fragilis* and *Ch. mcsnili* should be included in the list of potential pathogens. The pathogenic power of *E. nana*, *I. butschlii*, *Trichomonas*, *Embadomonas*, and *Enteromonas* was not revealed by his statistics.

II. J. SIMS.

THOMAS, G. L. Metastasis to bone in gastrointestinal malignancy. Surg. Clinics N. Am., 692 (June) 1946.

Out of 168 cases of metastatic carcinoma to the bony skeleton, only 11 cases were noted

with primary lesions in the digestive tract, and these were in the terminal phase of the disease in most instances.

A case of a 69 year-old women, with a pathologic inter-trochanteric fracture of the right hip showing evidence of femoral metastasis is reported. After admission, a primary carcinoma of the cecum was found. The hip fracture was managed by internal fixation and healed satisfactorily. The primary malignancy in the cecum and the metastases were treated by a right colectomy with a primary side-to-side ileo-transverse anastomosis. The patient has been completely comfortable for more than a year.

FRANK G. VAL DEZ.

TENTATIVE PROGRAM OF THE SCIENTIFIC SESSION

THE AMERICAN GASTROENTEROLOGICAL ASSOCIATION

MEETING IN ATLANTIC CITY, JUNE 9 AND 10 AT THE CLARIDGE HOTEL

MONDAY, JUNE 9, 1947

MORNING SESSION 9:30 A.M.

I. Studies on the Liver

1. The thymol turbidity test as a measure of liver disease. Harry Shay, J. Edward Berk, and Herman Siplet (by invitation), Philadelphia, Pennsylvania. 10 Minutes.
2. A study of the newer liver function tests including particularly the thymol turbidity and flocculation tests in individuals with induced virus hepatitis. John R. Neefe, Minneapolis, Minnesota, and (by invitation) John G. Reinhold and E. Reid Bahnson, Philadelphia, Pennsylvania. 10 Minutes.
3. Aspiration liver biopsy. Leon Schiff, and, (by invitation) Karl Kumpe, William Molle, Harold Steinberg, Edward Gall, and Ralph Johansmann, Cincinnati, Ohio. 10 Minutes.
4. Peritoneoscopic biopsies in hepatic diseases. George Gordon McHardy, New Orleans, Louisiana. 10 Minutes.
5. A study of phospholipid production in human beings with various types of liver disease by using radioactive phosphorus. William M. Balfour (by invitation) and M. W. Comfort, Rochester, Minnesota. 10 Minutes.
6. The role of the sex hormones in liver disease with observations on the treatment of cirrhosis of the liver with testosterone. B. D. Rosenak, Rollin H. Moser, and Byron Kilgore (by invitation), Indianapolis, Indiana. 10 Minutes.
7. The use of a high fluid intake and a low-sodium acid-ash diet in the management of portal cirrhosis of the liver with ascites. John A. Layne and (by invitation) F. R. Schemm, Great Falls, Montana. 10 Minutes.
8. Histologic changes in livers of patients with cirrhosis treated with Methionine. A. J. Beams and (by invitation) Elizabeth T. Endicott, Cleveland, Ohio. 10 Minutes.
Discussion: Chester M. Jones, Cecil J. Watson, Albert M. Snell, Daniel H. Lobby.

- II. 9. Chronic Jaundice not due to extrahepatic obstruction. John T.

McMichael, Professor of Medicine, British Post-Graduate Medical School, University of London, and S. P. V. Sherlock, London, England (by invitation).

III. Acute Enteritis

10. *Salmonella*—A cause of chronic bacterial dysentery. Daniel N. Silverman and (by invitation) Alan Leslie, New Orleans, Louisiana. 10 Minutes.
11. *Salmonellosis*—Experiences in military and civilian practice. Lucian A. Smith, Rochester, Minnesota. 10 Minutes.
12. Bacillary dysentery and chronic ulcerative colitis in connection with World War II. Joseph Felsen and (by invitation) William Wolarsky, New York, N. Y. 10 Minutes.
13. A survey on amebiasis. Lowell D. Snorf, Evanston, Illinois, and (by invitation) Betty Howard and Eliot E. Foltz, Chicago, Illinois. 10 Minutes.

Discussion: Philip W. Brown, Thomas T. Mackie.

MONDAY, JUNE 9, 1947

AFTERNOON SESSION, 2:00 P.M.

14. Personality disorders in gastroenterology. Albert J. Sullivan, and (by invitation) Thomas E. McKell, New Orleans, Louisiana. 10 Minutes.
Discussion: T. Grier Miller.
15. Observations on starvation edema in anorexia nervosa. A clinical study including the values for serum protein and the effect of forced feeding. John M. Berkman, James F. Weir, and (by invitation) E. J. Kepler, Rochester, Minnesota. 10 Minutes.
16. The injection treatment of esophageal varices. Cecil O. Patterson (by invitation) and Milford O. Rouse, Dallas, Texas. 10 Minutes.
Discussion: Edward B. Benedict, Herman J. Moersch.
17. Cardiospasm—A roentgenologic study of motor activity. Frederic E. Templeton, Seattle, Washington. 10 Minutes.
18. Gastric polyps. James B. Carey, Minneapolis, Minnesota. 10 Minutes.
19. Pernicious anemia. A gastroscopic survey. Leo L. Hardt, and (by invitation) Steven O. Schwartz and Frederick Steigman, Chicago, Illinois. 10 Minutes.
Discussion: Rudolf Schindler.
20. Carcinoid tumors of the small bowel. John B. D'Albora, and (by invitation) Alfred P. Ingegno, Brooklyn, New York. 10 Minutes.

21. Diagnosis of malignant cells in effusion fluids. Analysis of 200 cases. Dorothy Nagel Shaver, Charles F. Becker, and Kornel Terplan (by invitation), and A. H. Aaron, Buffalo, N. Y. 10 Minutes.
- IV. Symposium: Physiologic Phenomena.
 22. Gastric secretion before and after lobotomy. John A. Reed, Washington, D. C. 10 Minutes.
 23. A study of pressure relations in the pyloric sphincter region and their influence on gastric evacuation. J. Paul Quigley and Daniel A. Brody (by invitation), Memphis, Tennessee. 10 Minutes.
 24. Pharmacology of the sphincter of Oddi. H. Necheles, and M. Eisenstein (by invitation), Chicago, Illinois. 10 Minutes.
 25. Studies on the gall bladder in the unanesthetized dog before and after vagotomy. J. Earl Thomas, and (by invitation) W. J. Snape, Philadelphia, Pennsylvania. 10 Minutes.Discussion: A. C. Ivy.

EXECUTIVE SESSION

TUESDAY, JUNE 10, 1947

MORNING SESSION, 9:00 A.M.

- V. 26. The Fiftieth Anniversary of the American Gastroenterological Association. (By its historian.) Franklin W. White, Boston, Massachusetts.
- VI. 27. Presidential Address. Walter Lincoln Palmer, Chicago, Illinois.
- VII. Symposium: Ulcerative colitis.
 28. The course of "non-specific" ulcerative colitis. Joseph B. Kirsner and William E. Ricketts, Chicago, Illinois. 10 Minutes.
 29. An evaluation of the clinical management of chronic ulcerative colitis. Everett D. Kiefer, Boston, Massachusetts. 10 Minutes.
 30. The principle of "colonic rest" applied to the treatment of chronic ulcerative colitis. Thomas E. Machella and T. Grier Miller, Philadelphia, Pennsylvania. 10 Minutes.
 31. The chemotherapy of ulcerative colitis. Herman M. Pollard, Ann Arbor, Michigan. 10 Minutes.
 32. Alterations of the function of the colon in man under stress. Thomas P. Almy, Fred Kerns, and Beatrice Berle, New York, N. Y. (by invitation). 10 Minutes.
 33. Psychiatric factors in ulcerative colitis. George E. Daniels, New York, N. Y. (by invitation). 10 Minutes.

34. Surgical treatment of ulcerative colitis. Richard B. Cattell, Boston, Massachusetts (by invitation). 10 Minutes.
 35. Restoration of intestinal continuity following complete transverse ileostomy for "non-specific" ulcerative colitis. Moses Paulson and (by invitation) Henry N. Harkins, Baltimore, Maryland. 10 Minutes.
- Discussion: Burrill B. Crohn, Chester M. Jones, Sara M. Jordan, J. A. Bargen.

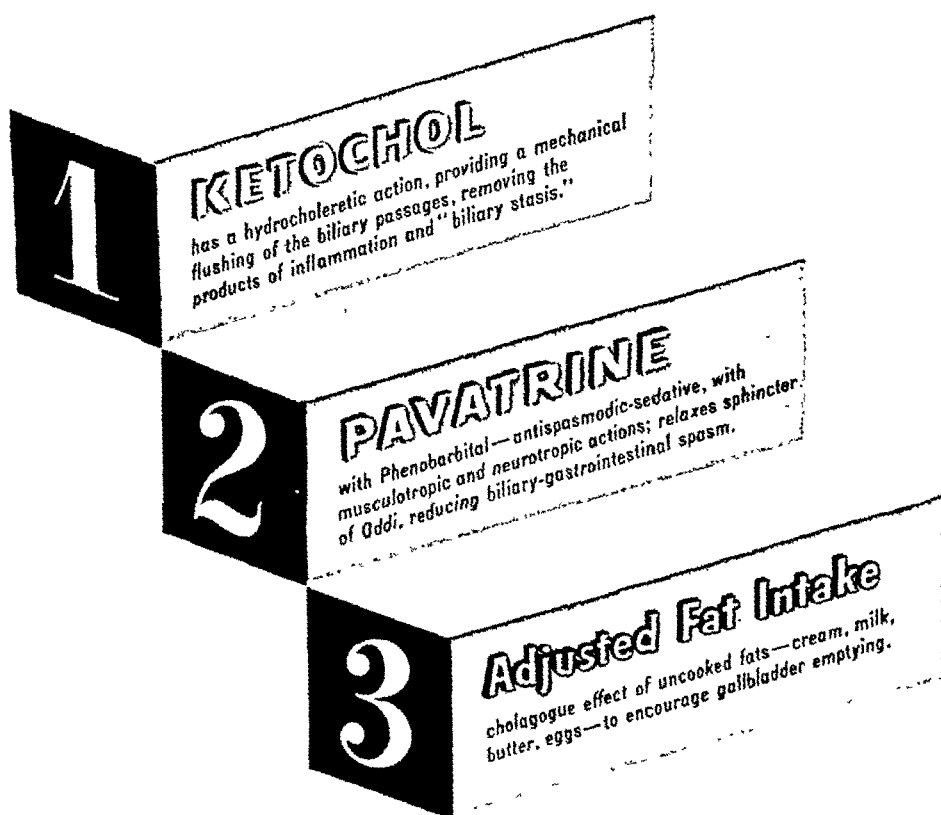
TUESDAY, JUNE 10, 1947

AFTERNOON SESSION, 2:00 P.M.

- VIII. 36. Studies on gastric mucus. Sir Howard Florey, William Dunn Professor of Pathology, Oxford University (by invitation).
- IX. Symposium: Peptic Ulcer.
37. Activities of the National Committee for the Study of Peptic Ulcer of the American Gastroenterological Association. David J. Sandweiss, Detroit, Michigan. 10 Minutes.
 38. Recurrence in duodenal ulcer under medical management. Charles A. Flood, New York, N. Y. 10 Minutes.
 39. Gastro-duodenal hemorrhage; clinical, roentgenologic and pathologic correlation. Burrill B. Crohn and (by invitation) Richard H. Marshak and David Galinsky, New York, N. Y. 10 Minutes.
 40. Protein hydrolysates in peptic ulcer. Bruce Kenamore, St. Louis, Missouri. 10 Minutes.
 41. The effect of Enterogastrone concentrates on the rate of healing of ulcers produced by surgical excision in the rabbit's stomach. M. I. Grossman, R. Villarreal, G. A. Westphal, Jr. (by invitation), and Arthur J. Atkinson and A. C. Ivy, Chicago, Illinois. 10 Minutes.
 42. Some observations on the mechanism of relief of ulcer distress by vagotomy. Lester R. Dragstedt, Chicago, Illinois. 10 Minutes.
 43. Bilateral vagotomy in the treatment of peptic ulcer. E. N. Collins, and (by invitation) C. W. Stevenson, Cleveland, Ohio. 10 Minutes.
 44. The function of the stomach as observed in fistulous human subjects, with special reference to the action of drugs and the effects of vagotomy. Stewart Wolf and (by invitation) Harold G. Wolff, New York, N. Y. 10 Minutes.
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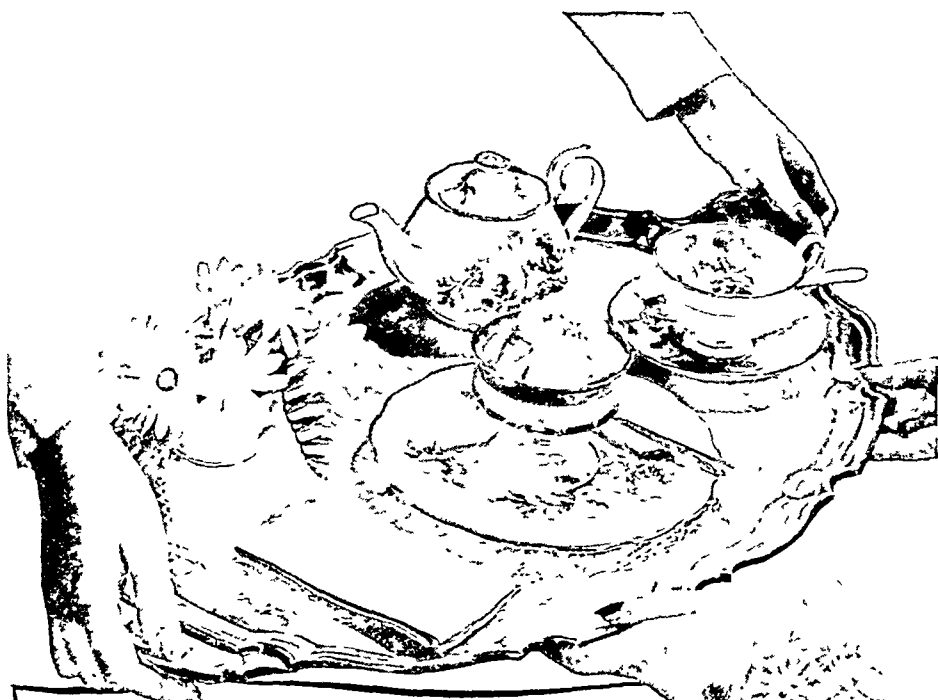
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Those who are interested in obtaining such instruction should write promptly to the person or school of their choice, because in most instances the number of students who can be accommodated is limited.

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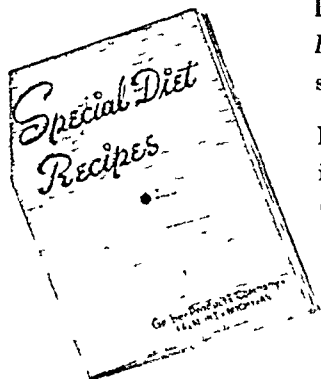


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